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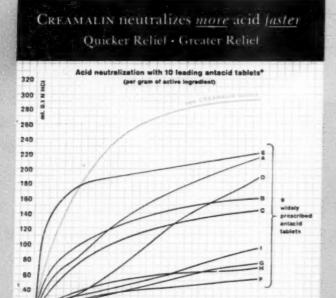
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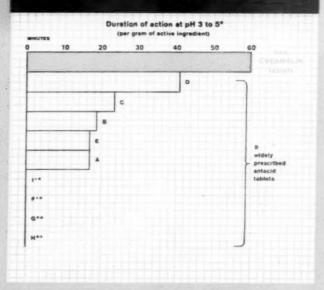
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The American Journal of Medicine

Vol. XXVI JUNE 1959 No. 6

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Editorial

The Development of the Use of Iron in Hypochromic Anemia

ARTHUR L. BLOOMFIELD 827

Clinical Studies

An Evaluation of Intermittent Peritoneal Lavage

COMDR. P. D. DOOLAN, W. P. MURPHY, JR., LT. R. A. WIGGINS, N. W. CARTER, LT. W. C. COOPER, Lt. COMDR. R. H. WATTEN

and E. L. ALPEN 831

Despite the increasing use of hemodialysis and, for reduction of threatening hyperkalemia, of resins in the management of uremic states, there is a place for intermittent peritoneal lavage, as this article attests. One of the major obstacles to the use of this procedure, kinking or blockage of the intraperitoneal tube, has been largely obviated by the authors through the development of a new tube, and they have introduced other details of procedure which reduce the danger of peritonitis and enhance the value of peritoneal lavage. By way of illustration of these advances, ten cases are cited, including some of acute suppression of urine, acute glomerulonephritis and chronic renal insufficiency.

Metabolic Alterations During Hemodialysis with the Disposable Coil Artificial Kidney GLENN D. LUBASH, BURTON D. COHEN, WARREN S. BRAVEMAN,

ALBERT L. RUBIN AND E. HUGH LUCKEY

In view of the expanding use of hemodialysis, notably of the Kolff disposable twin coil unit, a clearer understanding of what is accomplished, in metabolic terms, is desirable. The present study summarizes the changes effected in uremic patients with respect to blood urea nitrogen, plasma and red blood cell volume, and plasma potassium, bicarbonate, sodium, chloride, calcium, phosphorus, and osmolality. Impressive correction of derangements in electrolytes and fluid volume can be achieved as the experience of these and other investigators well demonstrates. Some of the many precautions which must be observed to obtain such good results in hemodialysis are appropriately stressed.

The Effect of Chlorothiazide on Renal Excretion of Electrolytes and Free Water
HENRY O. HEINEMANN, FELIX E. DEMARTINI AND JOHN H. LARAGH 853

The clearance data presented reaffirm the different effects of chlorothiazide and meralluride as diuretic agents. Chlorothiazide causes some reduction in glomerular filtration, a greater increase in solute output but without greater urine flow (no increase in free water clearance), and a larger

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NEEDS STENISONE TO RELIEVE HER SYMPTOMS
...YET AVOID INSIDIOUS SIDE EFFECTS

Here is a clinical portrait of the Menopausal Arthritic and her strange new problems which, up to now, have eluded simplified therapy:

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excretion of potassium. To explain these differences it is postulated that whereas meralluride acts only in the proximal tubule, chlorothiazide affects the reabsorption of sodium and chloride both in the proximal and more distal segments of the nephron. The clinical implications of these differences are briefly indicated, and the advantage of conjoint use of both diuretics in certain circumstances is pointed out.

Body Fluid Alterations During the Development of and Recovery from Hyponatremia in Heart Failure John R. Jaenike and Christine Waterhouse

It is now quite clear that hyponatremia in heart failure usually is dilutional, in many cases apparently due to primary water retention in excess of fixed cation, which also may be excessive. This is confirmed in the present balance studies, which offer further evidence of disturbed distribution of water and electrolytes between cellular and extracellular fluid in some cases. These latter abnormalities probably derive from some basic derangement in cellular metabolism in heart failure, the nature of which is still quite obscure. Applying these principles to management, by appropriate use of diuretics and water restriction, and eschewing the use of hypertonic saline solutions, it was possible to improve not only the sodium levels of the blood plasma but also the clinical status of the patient.

Salicylate Intoxication with Special Reference to the Development of Hypokalemia

EUGENE D. ROBIN, ROBERT P. DAVIS AND SEARLE B. REES 869

Six cases of poisoning by massive doses of salicylates are presented with details of the acid-base balance. An analysis of the respiratory alkalosis and metabolic acidosis is made with particular emphasis on the hitherto little appreciated finding of hypokalemia. Adequate potassium replacement is necessary. Other problems including renal damage, central nervous system symptoms, hypoprothrombinemia, and fever are also discussed. The therapeutic implications are described.

Pheochromocytoma Associated with Multiple Neurofibromatosis and Intracranial Hemangioma R. Cecil Chapman, V. Erick Kemp and Isabel Taliaferro 883

Attention was called in this Journal some years ago to the intriguing occasional association of neurofibromatosis with pheochromocytoma. The present study cites additional examples from the literature and from the authors' own experience, also the association with Hippel-Lindau's disease. The coincidence of these disorders occurs often enough to have diagnostic significance.

Studies in Disorders of Muscle. xII. Myopathy Due to the Administration of Therapeutic Amounts of 17-Hydroxycorticosteroids

GERALD T. PERKOFF, ROBERT SILBER, FRANK H. TYLER, G. E. CARTWRIGHT AND M. M. WINTROBE

As in spontaneous Cushing's syndrome, the hyperadrenocorticism associated with administration of adrenocortical hormones may be manifested by muscle weakness which can reach alarming, indeed incapacitating, proportions. If the origin of the muscle weakness and atrophy is not recognized, but attributed to the underlying disease and the dosage of corticosteroids therefore increased,

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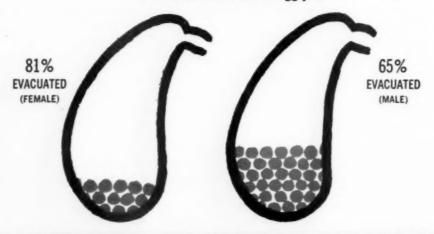
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*Source: Lichtman, S. S.: Diseases of the Liver, Gallbladder and Bile Ducts, ed. 3, Philadelphia, Lea & Febiger, 1953, vol. 2, p. 1178.

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much harm may be done; whereas reduction in the dosage of steroid hormones, if possible, soon is followed by restoration of muscle strength. The precise mechanism of steroid myopathy was not disclosed by this study, despite a variety of chemical examinations and muscle biopsy (which showed little intrinsic change in the muscles). Potassium depletion presumably is not a significant factor since all the patients of this study received potassium supplementation.

Review

"Psychogenic" Pain and the Pain-Prone Patient George L. Engel 899

Some pain patterns are easily recognized and often useful indeed in diagnosis but others, particularly "psychogenic" pain patterns, leave most of us so confused or frustrated that we are apt to dismiss them as "merely imaginary" and thus miss implications which are of great diagnostic significance even if not "somatic." It is this aspect of pain which is particularly illuminated in the present study. The pain-prone patient, it is brought out, may be expressing guilt, identification with some other person, a masochistic character structure in which pain is pleasurable, frustration in failure of aggressive drives, or other psychological stresses. The pain pattern may offer an important clue to the presence of conversion hysteria, depressed states, hypochondriasis and paranoid schizophrenia. These and many other points of interest are brought out; many cogently illustrated by patient histories, in a discussion well worth thoughtful reading.

Clinicopathologic Conference

Clinicopathologic Conference (Washington University School of Medicine).

Case Reports

- Cardiopulmonary Insufficiency Associated with Myotonic Dystrophy
 - KAYE H. KILBURN, JOHN T. EAGEN AND ALBERT HEYMAN 92

In this well studied case, the usual manifestations of myotonic dystrophica were accompanied by somnolence, cyanosis, Cheyne-Stokes respiration and cardiac arrhythmias. The latter symptoms were found to be due to alveolar hypoventilation, which evidently may be a consequence of myotonic dystrophy, as of other neuromuscular disorders involving the respiratory musculature.

Idiopathic Hypercalcemia Donald Gribetz and Bernard S. Wolf 936

A case of unusual interest.

Massive Metastatic Pulmonary Calcinosis in a Case of Multiple Myeloma

Walter B. Goldfarb 945

An unusual complication of multiple myeloma.

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REFERENCES: • 1. Freyberg, R. H.; Berntsen, C. A., Jr., and Hellman, L. Arth. & Rheum. 1:215 (June) 1958. • 2. Sherwood, H., and Cooke, R. A.: J. Allergy 28:97 (March) 1957. • 3. Shelley, W. B.; Harun, J. S., and Pillsbury, D. M.: J.A.M.A. 167:959 (June 21) 1958. • 4. Dubois, E.L.: California Med. 89:195 (Sept.) 1958. • 5. Hartung, E.F.: J.A.M.A. 167:973 (June 21) 1958.



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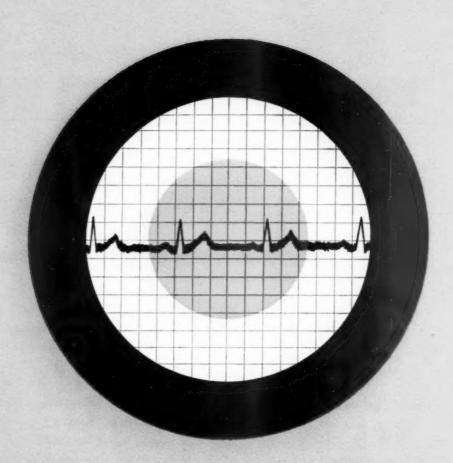
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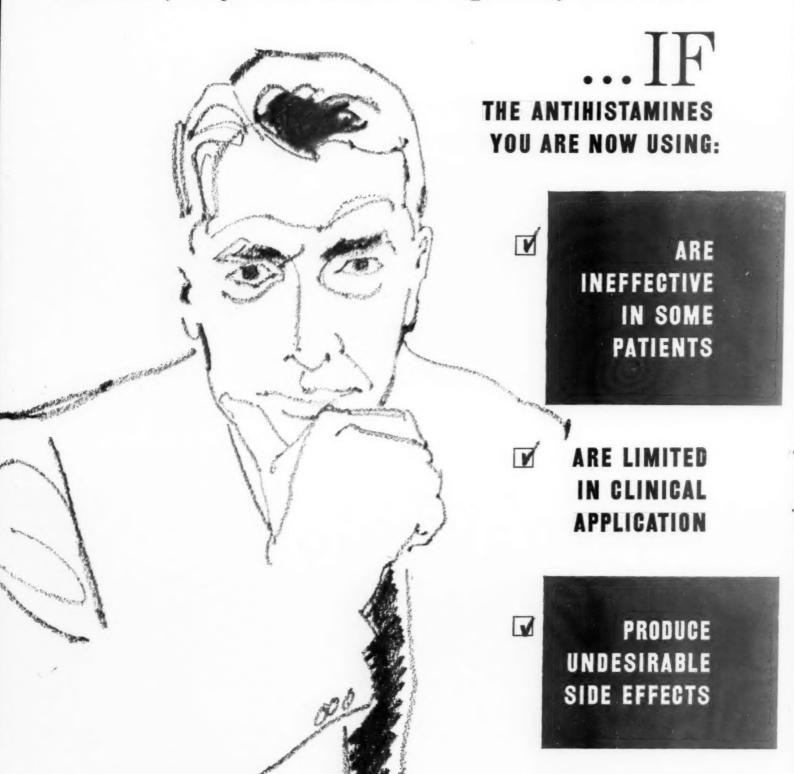
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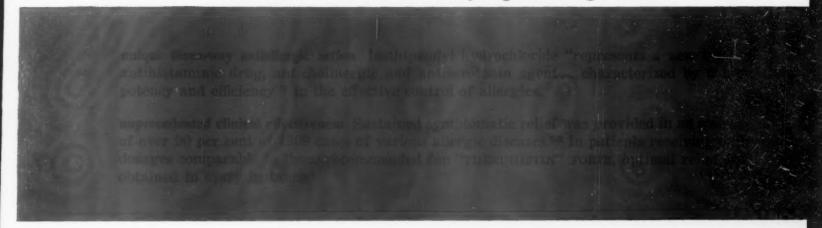
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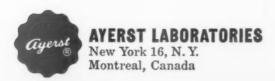
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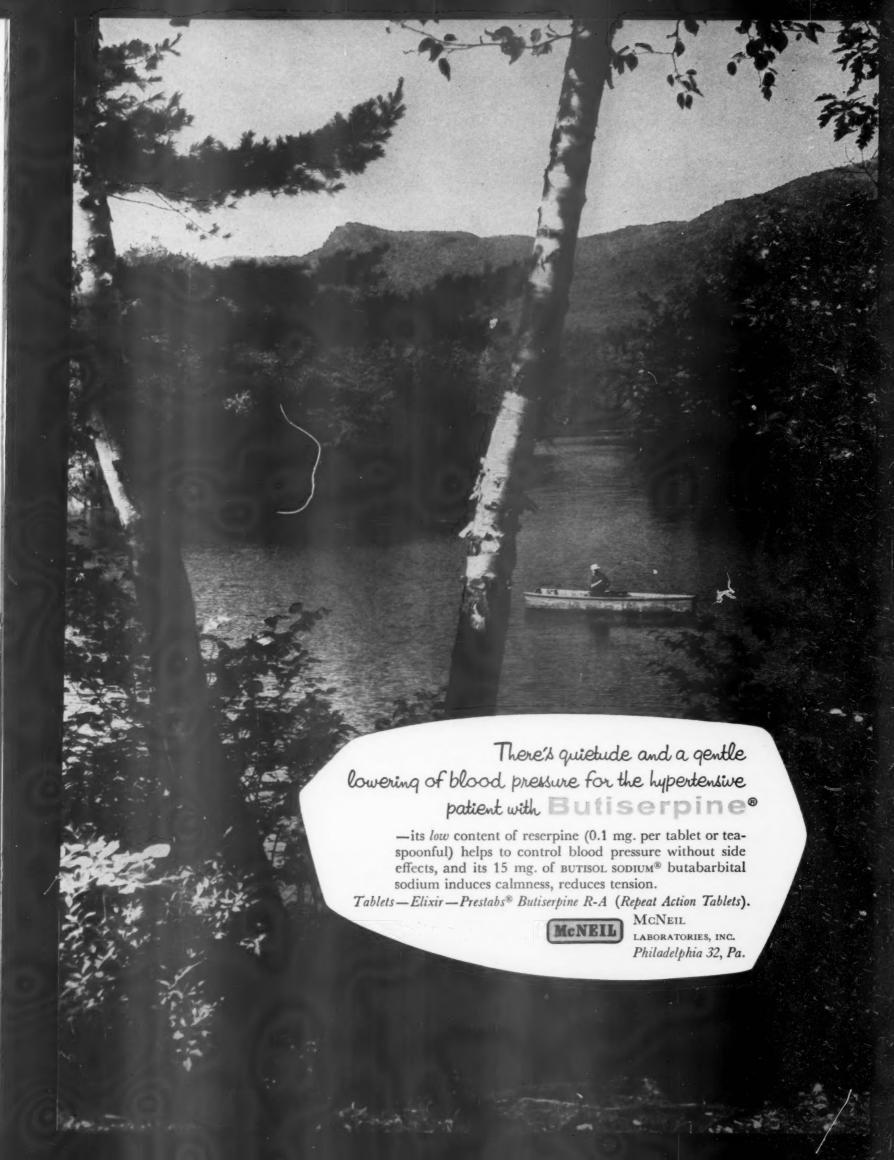
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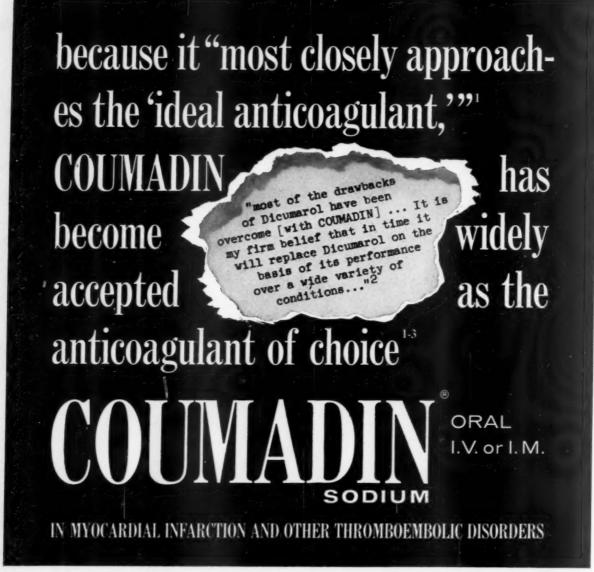
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After more than five years' clinical experience, it has been concluded: "In my opinion, Warfarin sodium [COUMADIN] is the best anticoagulant available today."³

COUMADIN CONSISTENTLY PROVIDES

rapid and sustained effect with low dosage \cdot high predictability \cdot ease of control for long periods \cdot low incidence of "escape" \cdot equal effectiveness by oral or parenteral routes \cdot reduced need for frequent prothrombin time determinations after initial dosage adjustment \cdot ready reversibility with vitamin K_1

Complete Information and Reprints on Request



ENDO LABORATORIES Richmond Hill 18, New York

TABLETS

For oral administration—2 mg., lavender, scored; 5 mg., peach, scored; 10 mg., white, scored; 25 mg., red, scored.

INJECTION

For parenteral administration— Single Injection Units, consisting of one vial, 75 mg., and one 3-cc. ampul Water for Injection.

AVERAGE DOSE

Initial, 50 mg. Maintenance, 5-10 mg. daily, as indicated by prothrombin time determinations.

COUMADIN (warfarin) Sodium manufactured under license from the Wisconsin Alumni Research Foundation—developed for clinical use by Endo.

References: 1. Baer, S., et al.: J.A.M.A. 167:704, 1958. 2. Link, K. P.: Circulation 19:97, 1959. 3. Meyer, O. O.: Postgrad. Med. 24:110, 1958.

specific for situational stress

PHENERGAN aids in carrying your patients through difficult periods of stress. It creates a state of quiescence without depressing vital functions. Because of its many actions and uses, Phenergan is used extensively in obstetrics, surgery, and in wide-ranging areas of medicine.

versatile in action

Psychic sedative

Antiemetic

Antihistaminic

Analgesic and narcotic potentiator

indications:

Nausea and vomiting

Motion sickness

Surgical sedation

Obstetrical sedation

Oral surgery and dental procedures

Allergic reactions

PHENERGAN®

HYDROCHLORIDE

Promethazine Hydrochloride, Wyeth

INJECTION • TABLETS • SYRUP • SUPPOSITORIES

Comprehensive literature supplied on request

Motion sickness Nausea and vomiting



Surgical and obstetrical sedation



Allergic reactions



in urticaria and pruritus

STARIL provides:



SPECIFIC ANTIHISTAMINIC **EFFECT**

in the treatment of a variety of skin disorders commonly seen in your practice.

"While some of the tranquilizers are only partially effective as far as antiallergic activities are concerned ... [hydroxyzine] has been found, by comparison, to be the most potent thus far . . . "2

"The most striking results were seen in those patients with chronic urticaria of undetermined etiology."1

... reduces-erythema, excoriation, and extent of lesions.1-4

PSYCHOTHERAPEUTIC POTENCY

for effective relief of tension and anxiety.1-4

Recommended Oral Dosage: 50 mg. q.i.d. initially; increase or decrease according to individual response.

Supplied as: Vistaril Capsules—25 mg., 50 mg. and 100 mg.

Vistaril Parenteral Solution—10 cc. vials and 2 cc. Steraject[®] Cartridges, each cc. contains 25 mg. hydroxyzine (as the HCl).



Plizer Science for the world's well-being

PFIZER LABORATORIES Division, Chas. Pfizer & Co., Inc. Brooklyn 6, New York



References: 1. Feinberg, A. R., et al.: J. Allergy 29:358 (July) 1958. 2. Eisenberg, B. C.: Clin. Med. 5:897-904 (July) 1958. 3. Robinson, H. M., Jr., et al.: J.A.M.A. 161:604-606 (June 16) 1956. 4. Robinson, H. M., Jr., et al.: South. M. J. 50:1282 (Oct.) 1957.

AN AMES CLINIQUICK"

CLINICAL BRIEFS FOR MODERN PRACTICE

what common oral lesions are often associated with uncontrolled diabetes?



Dryness of mouth; hyperemic swollen gums and mucous membranes; burning sensations in lips, tongue and palate, and loss of filiform papillae. *Source:* Sindoni, A., Jr.: Dental Clin. North America 2:459 (July) 1958.

for your routine screening...

"dip-and-read" tests

CLINISTIX for Glycosuria

ALBUSTIX° for Proteinuria

KETOSTIX® for Ketonuria

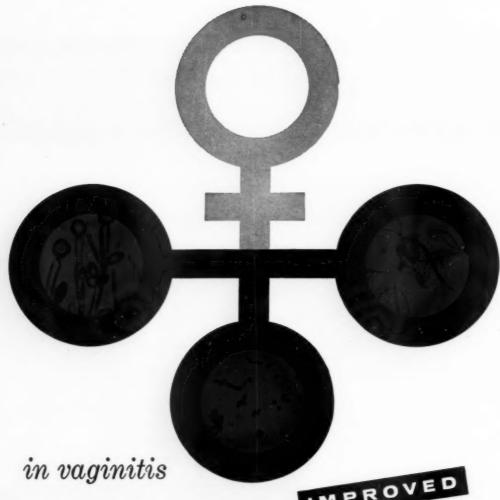
URISTIX for both Proteinuria and Glycosuria

PHENISTIX for Phenylketonuria

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TRICOFURONS

destroys all 3 principal pathogens

Whether vaginitis is caused by Trichomonas, Monilia or Hemophilus vaginalis—alone or combined—Tricofuron improved swiftly relieves symptoms and malodor, and achieves a truly high percentage of cultural cures, frequently in 1 menstrual cycle. Tricofuron improved provides: a new specific moniliacide MICOFUR® brand of nifuroxime, the established specific trichomonacide furoxone® brand of furazolidone and the combined actions of both against Hemophilus vaginalis.

1. Office insufflation once weekly of the Powder (MICOFUR [anti-5-nitro-2-furaldoxime] 0.5% and FUROXONE 0.1% in an acidic water-soluble powder base). 2. Continued home use twice daily, with the Suppositories (MICOFUR 0.375% and FUROXONE 0.25% in a water-miscible base).



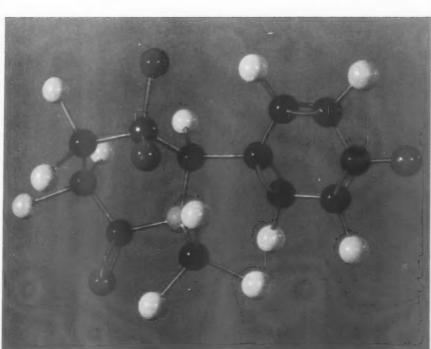
NITROFURANS—a new class of antimicrobials—neither antibiotics nor sulfonamides. O. N. EATON LABORATORIES, NORWICH, NEW YORK

for
low back pain
and
dysmenorrhea

I and copale the first true tranquilaxant*

Potent MUSCLE RELAXANT
... Equally effective as a TRANQUILIZER

* tran-qui-lax-ant (tran'kwi-lak'sant) [< L. tranquillus, quiet; L. laxare, to loosen, as the muscles]



Trancopal, a major development of Winthrop research, is a new, orally administered nonhypnotic central relaxant and tranquilizer. It relieves muscle spasm in a variety of musculoskeletal and neurologic conditions and also exerts a marked tranquilizing effect in anxiety and tension states.

Unrelated chemically to any other drug in current use, Trancopal offers a completely new major chemical contribution to therapeutics.

Clinical studies of over 4400 patients by 105 physicians proved Trancopal remarkably effective in musculoskeletal conditions, anxiety and tension states.

MUSCULOSKELETAL DISORDERS effective in

98

of 1570 documented cases of

LOW BACK PAIN

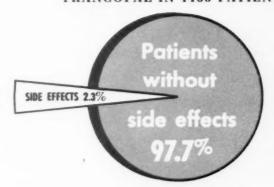
(LUMRAGO, SACROILIAC DISORDERS)

By relieving muscle spasm and pain, Trancopal permits early and active exercise and physical therapy to accomplish maximal benefits for rapid recovery.

TRANCOPAL the first true tranquilaxant

With Trancopal there is no clouding of consciousness, no euphoria or depression. Even in high dosage, there is no perceptible soporific effect. Because it does not irritate gastric mucosa, it can be taken without regard to mealtimes. Administration does not hamper work—or play. Blood pressure, pulse rate, respiration and digestive processes are unaffected by therapeutic dosage. Toxicity is extremely low. And Trancopal has a lower incidence of side effects than has zoxazolamine, methocarbamol or meprobamate.

INCIDENCE OF SIDE EFFECTS WITH TRANCOPAL IN 4483 PATIENTS



ANXIETY AND TENSION STATES

effective in

of 443 documented cases of

DYSMENORRHEA

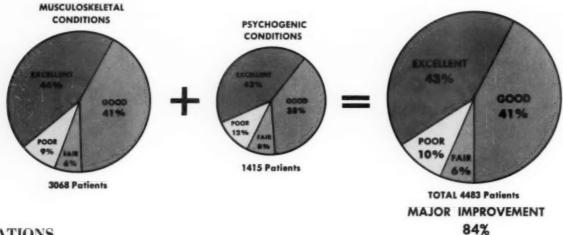
AND DEMENSTRUM TENSION

Because of its exceptional calmative property, Trancopal "... allows the patient to use his energies in a more productive manner in overcoming his basic problems."²

Dosage: 1 or 2 Caplets (100 mg.) orally three or four times daily. Relief of symptoms occurs in from fifteen to thirty minutes and lasts from four to six hours.

Thoroughly evaluated clinically...

Clinical studies of 4483 patients by 105 physicians¹ have demonstrated that Trancopal often is effective when other drugs have failed. From these studies it is evident that Trancopal can provide more help for a greater number of tense, spastic, and/or emotionally upset patients than can any other chemotherapeutic agent in current use.



INDICATIONS

Musculoskeletal

Low back pain (lumbago) Disk syndrome

Neck pain (torticollis, etc.) Fibrositis

Bursitis Ankle sprain, tennis elbow, etc.

Rheumatoid arthritis Myositis

Osteoarthritis Postoperative muscle spasm

Psychogenic

Anxiety and tension states Asthma

Dysmenorrhea Angina pectoris
Premenstrual tension Alcoholism

Supplied: Trancopal Caplets® (scored) 100 mg., bottles of 100.

References: 1. Collective Study, Department of Medical Research, Winthrop Laboratories. • 2. Ganz, S.E.: J. Indiana M. A. In press, • 3. Lichtman, A.L.: Kentucky Acad. Gen. Pract. J. 4:28, Oct., 1958.

The first true tranquilaxant and the first true tranquilaxant

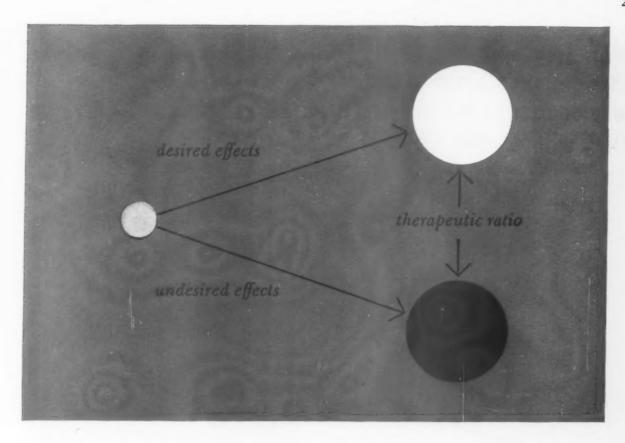
Potent

MUSCLE RELAXANT

...Equally effective as a

TRANQUILIZER

Winthrop LABORATORIES / New York 18, New York



The best therapeutic ratio in the steroid field confirmed by a comparative clinical study of

prednisone prednisolone methylprednisolone triamcinolone dexamethasone



in 65 rheumatoid arthritis patients:

"... It would appear from these comparative observations that methylprednisolone [Medrol] probably is the steroid of choice for initial trial in a patient with rheumatoid arthritis. It is potent, and displays a slightly improved 'safety' record, showing a reduced frequency of disturbing side effects compared with the other steroids."

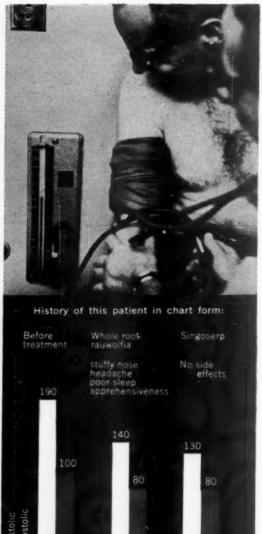


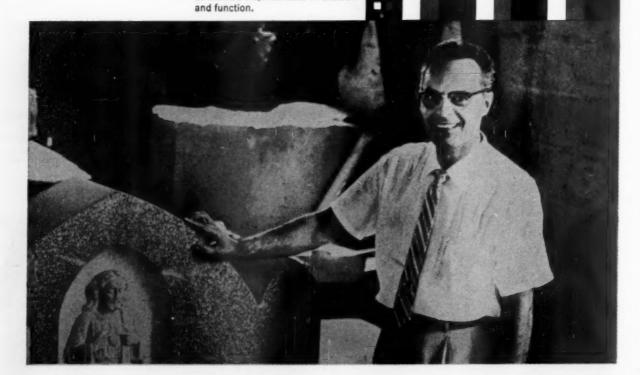
With Singoserp this patient's blood pressure was controlled for the first time without side effects

FROM THE FILES OF A PHILADELPHIA CARDIOLOGIST. PHOTOS USED WITH PERMISSION OF THE PATIENT.

Tombstone salesman had known hypertension for 16 years; rejected by U.S. Army because of high blood pressure. Whole root rauwolfia lowered pressure satisfactorily, but patient could not tolerate side effects.

Singoserp in a dosage of 0.5 mg. daily lowered his blood pressure to 130/80, produced no side effects. Patient feels well, works well, speaks of marked improvement in outlook





Clinical findings in 900 patients show the selective antihypertensive action of Singoserp

IN 735 PATIENTS, BLOOD PRESSURE FELL AN AVERAGE OF 30.7 mm. Hg:

- more than half of these patients suffered from moderate to severe hypertension
- more than half of the cases involved hypertension of at least 6 years' standing, with many histories of up to 20 years' duration

THE SIDE-EFFECTS PROBLEM WAS MINIMIZED IN MOST PATIENTS:

Chart shows gratifyingly low incidence of side effects in 233 patients given Singoserp with no other antihypertensive medication

Side Effect	Number	Per Cent
Lethargy	7	2.9
Headache	6	2.5
Gastrointestinal upset	3	1.2
Vertigo	2	0.8
Nasal congestion	1	0.4

DOSAGE:

In new patients: Average initial dose, 1 to 2 tablets (1 to 2 mg.) daily. Some patients may require and will tolerate 3 or more tablets daily. Maintenance dose will range from $\frac{1}{2}$ to 3 tablets (0.5 to 3 mg.) daily.

in patients taking other antihypertensive medication: Add 1 to 2 Singoserp tablets (1 to 2 mg.) daily. Dosage of other agents should be revised downward to a level affording maximal control of blood pressure and minimal side effects.







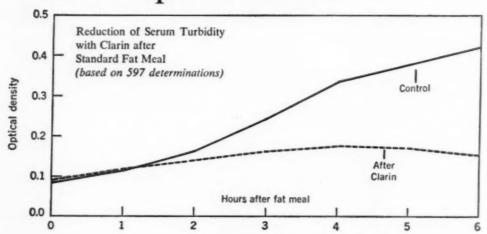
a major improvement in rauwolfia

a major advance in antihypertensive therapy

in the management of atherosclerosis

Clarin (sublingual heparin potassium, Leeming)

clears lipemic serum



Each time your patients eat a substantial fat-containing meal, lipemia results. Small amounts of injected heparin will help control this increased fat content in the blood, 1,2 but widespread adoption of this method has been hampered by its inconvenience, pain, cost and the necessity for periodic checks on blood clotting time.

Now, long-term preventive heparin therapy is practical for the first time with the introduction of CLARIN—which is heparin in sublingual form. Each CLARIN tablet contains 1500 I.U. of heparin potassium—a sufficient amount to clear lipemic serum without affecting coagulation mechanisms.^{3,4}

With one mint-flavored CLARIN tablet under the tongue after each meal, lipemia is regularly controlled, removing a constant source of danger to the atherosclerotic patient. He may eat safely, with less fear of dangerous results, without hard-to-follow diets.

The varied implications of CLARIN in beneficially affecting fat metabolism are obviously far-reaching. The relationship between heparin, lipid metabolism and atherosclerosis

may well be analogous to that between insulin, carbohydrate metabolism and diabetes mellitus.⁵

Use CLARIN to protect your atherosclerotic patients—the postcoronaries and those with early signs of coronary artery disease.

Indication: For the management of hyperlipemia associated with atherosclerosis.

Dosage: After each meal, hold one tablet under the tongue until dissolved.

Supplied: In bottles of 50 pink, sublingual tablets, each containing 1500 I.U. heparin potassium.

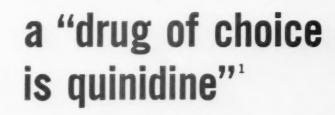
1. Council on Drugs, J.A.M.A. 166:52 (Jan. 4) 1958. 2. Hahn, P. F.: Science 98:19 (July 2) 1943. 3. Fuller, H. L.: Angiology 9:311 (Oct.) 1958. 4. Rubio, F. A., Jr.: Personal communication. 5. Engelberg, H., et al.: Circulation 13:489 (April) 1956.

*Trade Mark. Patent applied for.

Thos. Leeming & Co., Inc.

155 East 44th Street, New York 17, N. Y.





QUINAGLUTE° **DURA-TAB S. M.**

the only oral Sustained Medication* quinidine gluconate, 5 gr.

is a quinidine of choice'

in all CARDIAC ARRHYTHM

premature contractions, auricular tachycardia, flutter, fibrillation

- b.i.d. dosage each dose of Quinaglute Dura-Tab S.M. maintains uniform plasma levels up to 12 hours.
- · no night dose needed.
- · quinidine gluconate is more soluble, better absorbed and tolerated than quinidine sulfate.

Dosage: For conversion of auricular fibrillation to normal sinus rhythm, in most cases, 2 Quinaglute Dura-Tab S.M. tablets 3 to 4 times a day, for 2 to 3 days.

For maintenance 1 to 2 tablets every 10 to 12 hours.

Supplied: Bottles of 30, 100 and 250.

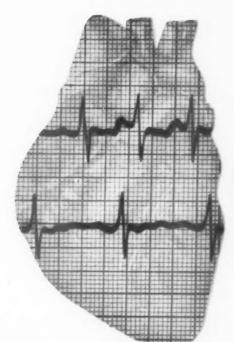
samples, reprint and detailed literature.

Now also available . . . INJECTABLE QUINAGLUTE® 10 cc. multiple dose vials, 0.08 Gm. Quinidine Gluconate per cc.

YNN PHARMACAL CORPORATION

5119 West Stiles Street, Philadelphia 31, Pa.

See us at Booth N-28 American Medical Association Convention, Atlantic City, New Jersey—June 8-12





1. Smith. J. M.: Lederle Bull. Symposium Report, 1:1, 1958.

2. Bellet, S., Finkelstein, D., and Gilmore, H.: A.M.A. Archives

Internal Med. 100:750, 1957.

*Patent Applied For

PAGE 867



Combined Orinase*-insulin therapy enables you to "stabilize" a surprising percentage of "brittle" diabetics

The primary indication for Orinase remains in the stable, maturity-onset diabetic in whom Orinase usually can fully replace insulin therapy. But now a further indication has developed from the cumulative data of the past several years: many labile diabetics, who cannot be managed on Orinase alone, can benefit from the *addition* of Orinase to their insulin regimen.

A major benefit-stabilization

In the labile diabetic who successfully responds to joint insulin-Orinase management, the "peaks and valleys" of erratic blood sugar levels are rarely observed. The addition of Orinase greatly reduces sudden and unexpected changes...tends to "stabilize" even the "brittle" diabetic.

A major benefit-lessened insulin needs

The Orinase-stabilized labile diabetic generally requires less insulin than before the inclusion of Orinase in his regimen. This lessening of insulin dosage is particularly advantageous in the patient who is insulin-dependent, but who reacts unfavorably — whether by lipodystrophy or otherwise—to insulin.

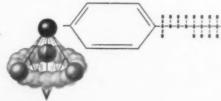
The derived benefits-less hypoglycemia, less anxiety, greater well-being

With stabilization, the hazards of shock or coma are diminished. Like the diabetic who is responsive to Orinase alone, the labile diabetic on combined therapy need no longer walk a slender tightrope between hypo- and hyperglycemia. The patient's fears are greatly lessened ...often to be replaced by the healthier outlook characteristic of *euglycemic* Orinase management.

*TRADEMARN, REG. U. G. PAT. GFF.— TOLBUTAMIDE, UPJOHN

Upjohn

The Upjohn Company Kalamazoo, Michigan AN EXCLUSIVE
METHYL "GOVERNOR"
PREVENTS
HYPOGLYCEMIA...
MAKES ORINASE
A TRUE
EUGLYCEMIC AGENT



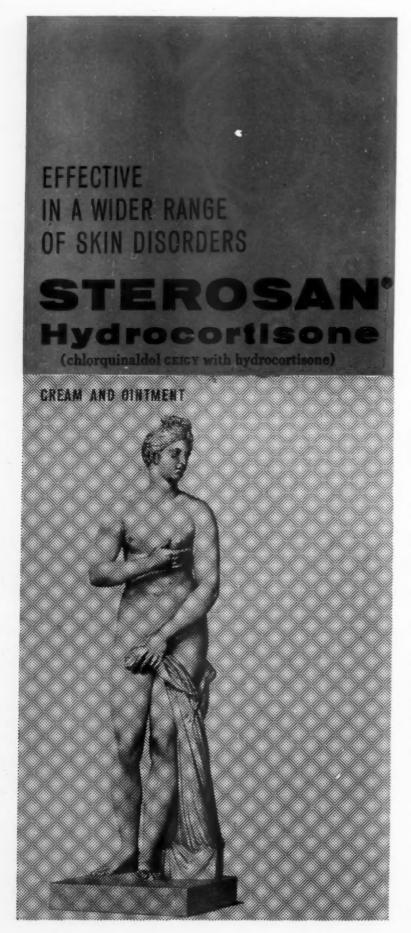


Nuclear-Chicago's experience in manufacturing medical instruments for detecting and measuring radioactivity began with the first hospitals to employ radioisotopes in diagnostic tests. From that time on, quality and dependability in design, manufacture, and service have made us the world's leading supplier of instruments for nuclear clinical and diagnostic use in medicine. Our specially trained medical sales and service force covers every state and most countries of the free world.

We invite you to call on our experience at any time for assistance in initiating radioisotope procedures or in modernizing your present facilities to cover new applications of radioisotopes. Our General Catalog R describes in detail over fifty medical instruments, accessories, and complete laboratories to cover every possible need in diagnostic applications of radioisotopes. If you would like to receive a personal copy for your files, just drop us a card or letter—there is no obligation.

Fine Instruments - Research Quality Radiochemicals





The highly effective antibacterial, antifungal STEROSAN combined with anti-inflammatory, antipruritic hydrocortisone provides rapid healing in a wider range of infective and allergic skin disorders. STEROSAN-Hydrocortisone is superior to either drug used alone and is effective where many antibiotic-hydrocortisone preparations fail.1 Virtually non-irritating and non-sensitizing, Sterosan-Hydrocortisone has the added advantage of being odorless, non-greasy, nonstaining, and scarcely perceptible on the skin.

1. Pace, B. F.: M. Rec. & Ann. 51:370, 1957.

STEROSAN®—Hydrocortisone (3% chlorquinaldol GEIGY with 1% hydrocortisone) Cream and Ointment. Tubes of 5 Gm. and 20 Gm. Prescription only.

GEIGY

ARDSLEY, NEW YORK

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FOR SALE:

ASSORTED FOOLPROOF DANDRUFF REMEDIES (SLIGHTLY USED)

Pity. So many nice starts on dandruff. So many expensive disappointments. Still, this man was lucky. He happened to mention it to his doctor, who happened to write a prescription for Selsun, which happened to be one of the few things in the world that can do him some good. So few think to mention it. (Dandruff a disease?) That's just when a word from you—and a prescription for Selsun—will be most appreciated. Obbott

SELSUN

(Selenium Sulfide, Abbott)

an ethical answer to a medical problem



ANEMIA IN THE MENOPAUSE, another indication Iberol...potent antianemia therapy plus the complete B-complex.

Obbott

when the response to other hypotensive agents is inadequate . . .

and further reduction of blood pressure is desirable . . .

adding ganglionic-blocking

INVERSINE

often makes possible a lessening of cardiovascular-renal damage, regression of the basic disease, and prolongation of life

"unnecessary delay must be avoided in establishing ganglion blockade in severe or malignant hypertension"

Beem, J. R., and Moyer, J. H.: Geriatrics 13:378, June 1958.

relieve high blood pressure and its manifestations

INVERSINE.

for moderate, severe, and malignant hypertension



"When employed under carefully controlled conditions with adequate attention to proper regulation of dosage, mecamylamine ['INVERSINE'] may be expected to reduce blood pressure effectively and to ameliorate various manifestations of hypertensive-cardiovascular disease. These include such symptoms as headache, dizziness, vertigo, hypertensive encephalopathy, cerebral or subarachnoid hemorrhage, retinopathy, cardiac hypertrophy and, in some cases, cardiac decompensation."

A.M.A. Council on Drugs, New and Nonofficial Drugs: Philadelphia, J. B. Lippincott Co., 1958, p. 285

A GREATLY IMPROVED GANGLIONIC BLOCKING AGENT

'INVERSINE'

- of the orally effective blocking agents, only 'INVERSINE' is completely and uniformly absorbed
- because it is uniformly absorbed, 'INVERSINE' provides predictable, reproducible effects with minimal day-to-day fluctuations
- · has a gradual onset of effect, reducing the likelihood of sudden drops in blood pressure
- effective in extremely low dosage (orally, 10 mg. 'INVERSINE' is approximately
 equivalent to 100 mg. pentolinium, 80 mg. chlorisondamine, 1000 mg. hexamethonium)
- has a long duration of action (6 to 12 hours or longer), permitting convenient dosage schedules
- · development of tolerance is not as pronounced as with other ganglionic blocking drugs
- · effective in many patients who do not respond to other ganglionic blocking drugs

pretreatment with 'Diuril', or 'Diuril' and rauwolfia, enhances therapy with 'Inversine'

"Pretreatment with chlorothiazide ['DIURIL'] and rauwolfia reduces the dosage requirement, augments blood pressure response, and moderates certain of the side effects of ganglion blocking agents. Although such basal therapy is advantageous, unnecessary delay must be avoided in establishing ganglion blockade in severe or malignant hypertension."

Beem, J. R., and Moyer, J. H.: Geriatrics 13:378, June 1958

dosage recommendations for new patients

1. Initiate therapy with 'DIURIL'

'DIURIL' is given in a dosage range of from 250 mg. twice a day to 500 mg. three times a day, depending on severity of the hypertension.

2. Add other agents

Other drugs (rauwolfia, 'INVERSINE', hydralazine, etc.) are added as necessary and their dosage adjusted according to patient response.

'INVERSINE' is given in the same manner whether used with other drugs or alone. Recommended initial dosage is 2.5 mg. twice a day, preferably after meals. May be increased by 2.5 mg. at intervals of no less than two days until desired response is obtained. In severe or urgent cases, the increments may have to be larger or more frequent, with the largest dose given preferably at noon or in the evening. 'INVERSINE' is extremely potent and should always be titrated according to the patient's orthostatic blood pressure response.

3. Adjust dosage of all medication

The patient must be observed frequently and careful adjustment of all agents should be made to determine optimal maintenance dosage.

Precautions: Side effects of 'INVERSINE' are essentially the same as those encountered with other ganglionic blocking agents. At the first sign of constipation, vigorous treatment must be initiated immediately since paralytic ileus may result if constipation is unchecked. Patients should be informed how to cope with postural hypotension should this occur. 'INVERSINE' is contraindicated in coronary insufficiency, organic pyloric stenosis and recent myocardial infarction. Additional information on 'INVERSINE' and 'DIURIL' is available on request.

Supplied: 'INVERSINE', tablets of 2.5 and 10 mg. Bottles of 100.

'DIURIL', tablets of 250 mg. and 500 mg. Bottles of 100 and 1000.



11/10

MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., PHILADELPHIA 1. PA.

INVERSINE and DIURIL are trademarks of Merck & Co., Inc.

helps them weather the hay fever season

BENADRYL

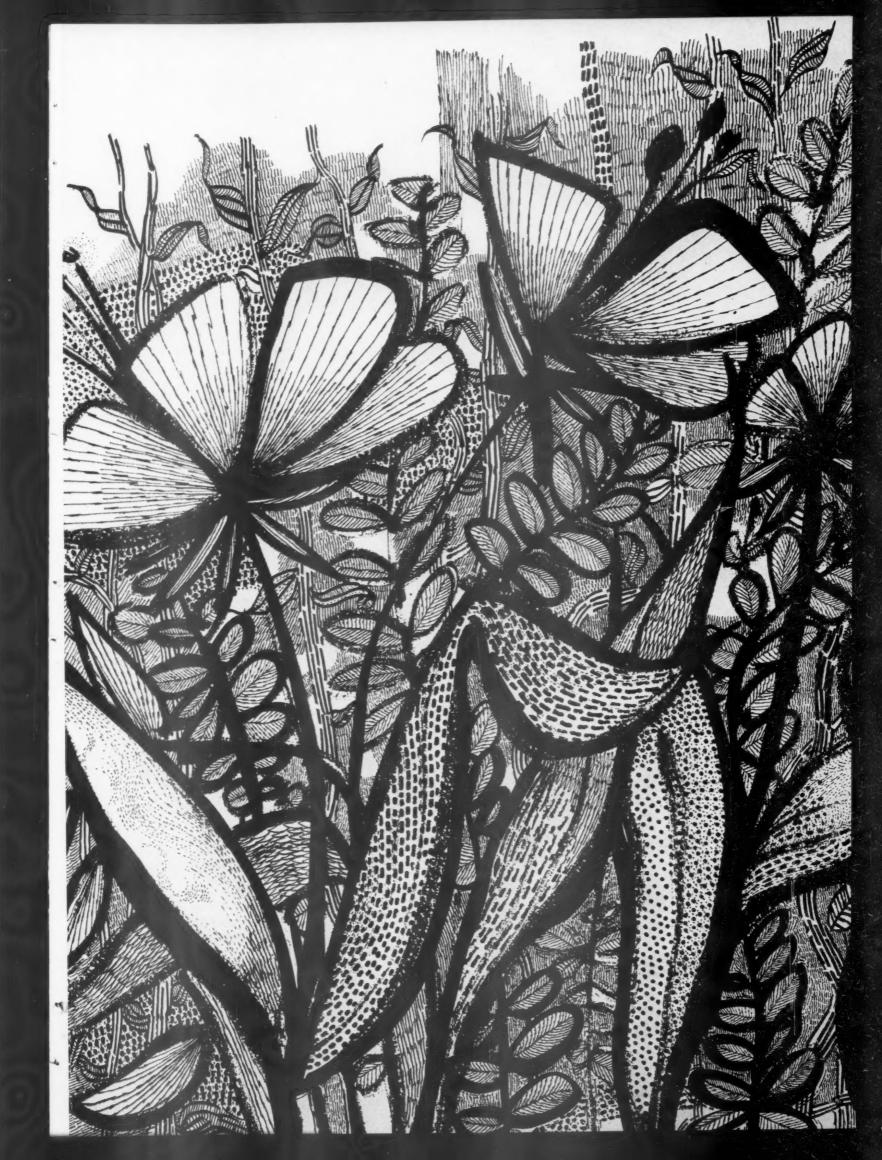
ANTIHISTAMINIC-ANTISPASMODIC

gives fast, comprehensive relief of allergic symptoms. At this time of year pollens from trees, grasses, or weeds cause distressing symptoms in allergic patients. You can help your patients to enjoy greater comfort during the hay fever season by prescribing BENADRYL. Its potent antihistaminic action rapidly relieves nasal blockage, rhinorrhea, sneezing, itching, and related allergic reactions, while its atropine-like antispasmodic action swiftly suppresses bronchial and gastrointestinal spasms. BENADRYL Hydrochloride (diphenhydramine hydrochloride, Parke-Davis) is available in a variety of convenient forms including: Kapseals,* 50 mg. each; Kapseals, 50 mg., with ephedrine sulfate, 25 mg.; Capsules, 25 mg. each; Elixir, 10 mg. per 4 cc.; and Emplets,* 50 mg. each, for delayed action. For parenteral therapy, BENADRYL Hydrochloride Steri-Vials,* 10 mg. per cc.; and Ampoules, 50 mg. per cc.



PARKE, DAVIS & COMPANY · DETROIT 32, MICHIGAN

95059





NEW A SENTRY FOR THE G.I. TRACT

protects against
hypersecretion • hypermotility
hyperirritability • hyperemotivity

anticholinergic / antispasmodic / tranquilizer

A remarkably long-acting anticholinergic. Only one 10 mg. dose of new long-acting oxyphencyclimine controls hypersecretion and spasm³ for 12 hours or more. In the most recent study at Cook County Hospital, investigators were impressed with its antisecretory effect, leading to prolonged periods of achlorhydria. 51 out of 57 patients with various G.I. disorders were relieved of symptoms on only 2 daily doses.

Plus ATARAX – the antisecretory tranquilizer. Not only does ATARAX modify tension—its added antisecretory action^{4,7-9} augments the efficacy of oxyphencyclimine. The combination, ENARAX, freed 100 out of 103 patients of G.I. symptoms.² Improvement was especially notable in cases of peptic ulcer, where the emotional factor figures so prominently.

"Side reactions were uncommon...." Selective postganglionic action on the G.I. tract minimizes side effects. Mouth dryness—the most common reaction—seldom reaches troublesome proportions. Each ENARAX tablet contains: Oxyphencyclimine HCl, 10 mg.; Hydroxyzine HCl (ATARAX®), 25 mg.

Dosage: One-half to one tablet twice daily—preferably in the morning and before retiring. The maintenance dose should be adjusted according to therapeutic response. Use with caution in patients with prostatic hypertrophy or glaucoma.

Supplied: In bottles of 60 black-and-white scored tablets.

			-	CTC
MIMILIE	A BE Y	V OF	E.A	SES

Clinical Diagnosis	Oxyphencyclimine1,8,0,	TENARAX 34
Peptic ulcer	440	48
Gastritis	16	17
Gastroenteritis		55
Colitis	37	
Duodenitis	6	3
Functional bowel syndrome	14	
Hiatus hernia (symptomatic) 16	1
Pylorospasm or cardiospasm	11	2
Irritable bowel	H H	41 10 -
Biliary tract dysfunctions	11	
Miscellaneous	7	29
Total number of patients	569	156
Clinical Results Excellent	445	150
Fair	56	2
Failure	68	6

- * Oxyphencyclimine alone—clinically effective in 87% after a year's
- † ENARAX (oxyphencyclimine plus ATARAX)—all successful cases in "excellent" category.

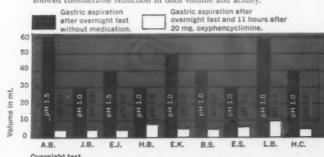
A SENTRY FOR THE G.I. TRACT (oxyphencyclimine plus ATARAX®)



one
tablet
at breakfast
one
tablet
at bedtime
for
full-time
relief

ACID REDUCTION AFTER OXYPHENCYCLIMINE THERAPY

Tests conducted in 9 representative ulcer patients after overnight fasts showed considerable reduction in both volume and acidity.



References: 1. Winkelstein, A.: Am. J. Gastroenterol., in press. 2. Leming, B. H., Jr.: Clin. Med. 6:423 (March) 1959. 3. McHardy, G., et al.: Paper presented at Postgraduate Course in Gastroenterology, University of California School of Medicine, San Francisco, Calif., January 27, 1958. 4. Strub, I. H., and Carballo, A.: To be published. 5. Pata in Roerig Medical Department files. 6. Steigmann, F.: To be published. 7. Schuller, E.: Gaz. des Höpitauk 10:391 (Apr. 10) 1957. S. Farah, L.: Internat. Rec. Med. 169:379 (June) 1956. 9. Harrisson, J. W. E., et al.: Paper presented at the 4th Pan-American Congress of Pharmacy and Biochemistry, Washington, D. C., November 3-9, 1957.



New York 17, N.Y. Division, Chas. Pfizer & Co., Inc. Science for the World's Well-Being

Whenever your Rx requires a sedative component...



widely compatible

Elix Thiamin HCl Elix Alurate, Ta... 3 iii (9000) M. Sig 3 ii three times a day before weals

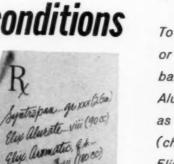
Rx FOR NERVOUS ANOREXIA

Alunate sedative hypnotic

Rx FOR NEURITIC PAIN

Combines prompt action, broad

margin of safety and virtual freedom from after-effects in a host of common conditions



Rx FOR SPASTIC DYSMENORRHE



Rx FOR INSOMNIA DUE TO PAIN

To avoid identification or abuse of the barbiturate component, Alurate is available as Elixir Alurate (cherry-red) and Elixir Alurate Verdum (emerald-green).

ALURATE® brand of aprobarbital.



Roche Laboratories

Division of Hoffmann-La Roche Inc. Nutley 10, New Jersey

"full-range"

a gl

in the management wild, moderate and severe did (juvenile and ce



Trademark, brand of Phenformin

DBI (N¹- β -phenethylbiguanide HCl) is an entirely new oral hypoglycemic compound, different in chemical structure, mode of action, and in spectrum of activity from the sulfonylureas. DBI is usually effective in low dosage range (50 to 150 mg. per day).

"full-range" hypoglycemic action

- DBI lowers elevated blood-sugar and eliminates glycosuria in *mild*, *moderate* and *severe* diabetes mellitus...

brittle diabetes, juvenile or adult— DBI combined with injected insulin improves regulation of the diabetes and helps prevent the wide excursions between hypoglycemic reactions and hyperglycemic ketoacidosis.

stable adult diabetes — satisfactory regulation of diabetes is usually achieved with DBI alone without the necessity for insulin injections.

juvenile diabetes – DBI often permits a reduction as great as 50 per cent or more in the daily insulin requirement.

primary and secondary sulfonylurea failures

- DBI alone, or in conjunction with a sulfonylurea, often permits satisfactory regulation of diabetes in patients who have failed to respond initially or who have become resistant to oral sulfonylurea therapy.

smooth onset — less likelihood of severe hypoglycemic reaction—DBI has a smooth, gradual blood-sugar lowering effect, reaching a maximum in from 5 to 6 hours, and a return to pre-treatment levels usually in 10 to 12 hours.

safety – DBI given daily to over 3,000 diabetics for varying periods up to nearly 3 years produced no form of clinical toxicity.

side reactions — side reactions produced by DBI are chiefly gastrointestinal and occur with increasing frequency at higher dosage levels (exceeding 150 mg. per day). Anorexia, nausea or vomiting may occur — but these symptoms abate promptly upon reduction in dose or withdrawal of DBI.

supplied -DBI, 25 mg. scored, white tablets - bottle of 100.

IMPORTANT—before prescribing DBI the physician should be thoroughly familiar with general directions for its use, indications, dosage, possible side effects, precautions and contraindications, etc. Write for complete detailed literature.

an original development from the research laboratories of

u.s. vitamin & pharmaceutical corporation

Arlington-Funk Laboratories, division 250 East 43rd Street, New York 17, N.Y.



VESPRIN made the difference

in anxiety and tension states / psychomotor agitation / phobic reactions / obsessive reactions / senile agitation / agitated depression / emotional stress associated with a wide variety of physical conditions

In the patient with anxiety and tension symptoms — Vesprin calms him down without slowing him up...and does not interfere with his working capacity. Vesprin permits tranquilization without oversedation, lethargy, apathy or loss of mental clarity.⁴

And Vesprin exhibits an improved therapeutic ratio—enhanced efficacy with a low incidence of side effects; no reported hypotension, extrapyramidal symptoms, blood dyscrasia or jaundice in patients treated for anxiety and tension.^{1,2,8}

dosage: for "round-the-clock" control – 10 mg. to 25 mg., b.i.d.; for "once-a-day" use – 25 mg. once a day, appropriately scheduled, for therapy or prevention. supply: Oral Tablets, 10, 25 and 50 mg., press-coated, bottles of 50 and 500; Emulsion (Vesprin Base) – 30 cc. dropper bottles and 120 cc. bottles (10 mg./cc.). references: 1. Stone, H.H.: Monographs on Therapy 3:1 (May) 1958. 2. Reeves, J.E. Postgrad. Med. 24:687 (Dec.) 1958. 3. Burstein, F.: Clinical Research Notes 2:3, 1959. 4. Kris, E.: Clinical Research Notes 2:1, 1959. Vesprint to transpullizer that fills a need in every major area of medical practice



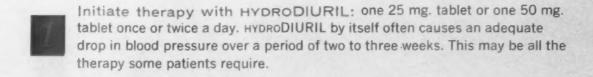
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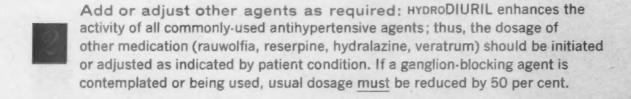
simplifies*and improves any regimen for hypertension

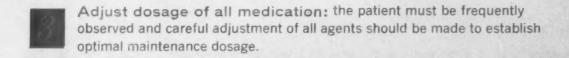


*it's as easy as 1, 2, 3 to use

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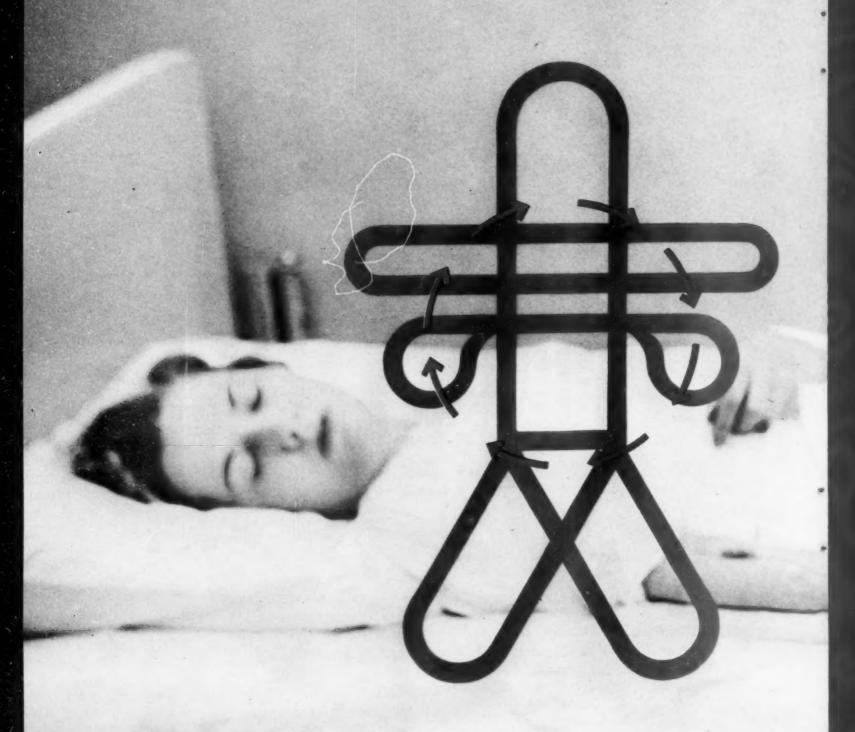
Supplied: 25 mg. and 50 mg. scored tablets HYDRODIURIL (Hydrochlorothiazide) bottles of 100 and 1,000.

Additional literature for the physician is available on request.

HYDRODIURIL is a trademark of Merck & Co., Inc. Trademarks outside the U.S., DICHLOTRIDE, DICLOTRIDE, HYDROSALURIC.



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DISSOLUTION OF CLOTS WITH

ACTASE

Fibrinolysin (Human)

THE OPENING OF A NEW EPOCH

in the treatment of thromboembolic disorders: THROMBOPHLEBITIS PULMONARY EMBOLISM



With ACTASE it is now possible to enhance plasma fibrinolytic activity. ACTASE is prepared from human plasma. It contains the active and purified form of the proteolytic enzyme fibrinolysin. "The clinical results after fibrinolysin infusion...have been consistently encouraging in terms of its apparent ability to dissolve a recently acquired intravascular clot." CLINICAL DATA





SPECIFIC THERAPY - lysis of the clot

thrombophlebitis . pulmonary embolism

ACTASE



Fibrinolysin (Human)

A NEW THERAPEUTIC AGENT

ACTASE "...may prove a safe and effective agent for achieving acute lysis of intravascular clot." In thrombophlebitis the benefits "...range from significant improvement to complete rapid relief, if adequate doses are administered."

"Pulmonary emboli, although notoriously difficult to evaluate clinically, respond well to plasmin [fibrinolysin]."²

ACTASE overcomes the disadvantages of earlier thrombolytic agents, which proved to be ineffective for intravenous use, or unsafe because of severe side reactions and lack of specificity.

Studies show that ACTASE, while maintaining

fibrinolytic activity, has no clinically significant effect on blood coagulation. "Anticoagulant drugs can be safely used simultaneously."

SAFETY IN CLINICAL USE

The only reaction observed with intravascular use of fibrinolysin has been a temperature rise in some patients. In one series³ of 141 patients, there was no febrile response in 35 per cent, a mild temperature rise in 42 per cent, and a severe febrile reaction in 23 per cent. Chilliness, nausea, vomiting, dizziness, headache and muscle pain may occur. The prophylactic administration of antipyretics^{1,4} and antihistamines,¹ or sedatives, may lessen and possibly prevent the febrile reaction.

CLINICAL RESULTS WITH FIBRINOLYSIN THERAPY

Source	Indication	Number of Patients	Results	
Moser ¹	Pulmonary embolism	8	4 patients showed beneficial effects	
Cliffton ²	Thrombophlebitis and pulmonary emboli	4	3 patients experienced complete relief	
ORTHO3	Pulmonary embolism	36	70% excellent; 24% questionable; 6% poor	
Moser ¹	Deep venous thrombophlebitis	18	"consistently encouraging"	
Cliffton ²	Venous thromboses	17	excellent response in 9 of 11 patients who received adequate dosage	
Cliffton ⁵	Peripheral venous thrombosis	12	improvement in all patients, ranging from subsidence to unequivocal lysis of the thrombus	
Moser ¹	Superficial thrombophlebitis	7	evidence of thrombolysis in 4 patients	
ORTHO3	Thrombophlebitis	171	65% excellent; 26% good; 9% poor	

ACTASE is given as an intravenous infusion over a period of two hours. Complete literature is available on request.

Packaging: ACTASE is supplied in vials containing 50,000 Fibrinolytic Units.

References: (1) Moser, K. M.: J.A.M.A. 167:1695 (Aug. 2) 1958. (2) Cliffton, E. E.: J. Am. Geriatrics Soc. 6:118, 1958. (3) Clinical Research Division, Ortho Pharmaceutical Corporation. (4) Ambrus, J. L., and others: Ann. New York Acad. Sc. 68:97 (Aug. 30) 1957. (5) Cliffton, E. E.: Ann. New York Acad. Sc. 68:209 (Aug. 30) 1957.

Ortho

ORTHO PHARMACEUTICAL CORPORATION . RARITAN, NEW JERSEY

your patient has high blood pressure plus one or more of these complications: anxiety congestive failure tachycardia edema/overweight control all the symptoms with just one prescription

new Esidrix T.M. Serbasile (hydrochlorothiazide and reserpine CIBA)

Combination Tablets

new Esidrix-Serpasil:



High blood pressure plus tachycardia

Therapy: Esidrix-Serpasil. Rationale: Heartslowing effect of Serpasil to prolong diastole, allow more time for recovery of myocardium, increase coronary blood flow, improve cardiac efficiency. Potentiated antihypertensive effect for greater blood pressure control.



High blood pressure plus congestive failure

Therapy: Esidrix-Serpasil. Rationale: Potent diuretic action of Esidrix to relieve edematous condition, improve cardiac status. Combined antihypertensive action of Esidrix and Serpasil for lowest blood pressure levels. Convenience of combination tablet medication for greater patient acceptance.

one prescription that controls high blood pressure plus its complications



High blood pressure plus edema/overweight

Therapy: Esidrix-Serpasil. Rationale: Diuretic effect of Esidrix to eliminate excess body fluids, bring patient to dry weight. Potentiated antihypertensive effects of Esidrix and Serpasil in combination. Convenience of 1-prescription therapy.

B.P.: 170/112 mm. Hg Nervous

Sweating palms



High blood pressure plus anxiety

Therapy: Esidrix-Serpasil. Rationale: Central action of Serpasil to calm the patient, shield him from environmental stress. Combined antihypertensive action of Esidrix and Serpasil for lowest blood pressure levels. Simplified dosage schedule.

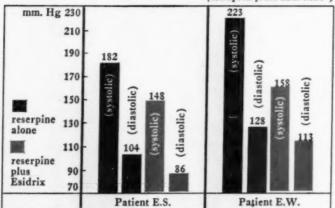
one prescription that controls high blood pressure plus its complications Esidrix-Serpasil Combination Tablets

A new antihypertensive combination—Esidrix-Serpasil is a combination of ESIDRIX^{T.M.} (hydrochlorothiazide CIBA), an improved analog of chlorothiazide developed by CIBA research, and SERPASIL® (reserpine CIBA). Each tablet combines the potent diuretic and mild antihypertensive effects of Esidrix with the antihypertensive, heart-slowing and calming effects of Serpasil.

Indications—Esidrix-Serpasil is indicated in all grades of hypertension, particularly when one or more of the following complications exist: anxiety, tachycardia, congestive failure, pitting edema, edema of obesity, other edematous conditions.

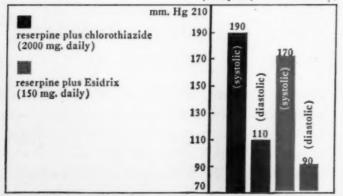
More effective than either drug alone—Investigators who have used the combination of hydrochlorothiazide and reserpine report that it is more satisfactory than either drug alone.

(Adapted from Maronde1)



More effective than chlorothiazide-reserpine combinations— Many patients resistant to chlorothiazide-reserpine therapy have shown significant clinical response when Esidrix-Serpasil was started. The blood pressure of patient shown below was only slightly reduced on chlorothiazide and reserpine. When Esidrix was substituted for chlorothiazide, lower blood pressure levels were achieved.

(Adapted from Greenstein2)



Dosage—Esidrix-Serpasil is administered orally in a dosage range of 1 to 4 tablets daily. Each tablet contains 25 mg. of Esidrix and 0.1 mg. of Serpasil. The total daily dose may be given after breakfast or in 2 or 3 divided doses. Dosage in every case should be individualized and adjusted to meet changing needs.

Since the antihypertensive effect of Serpasil is not immediately apparent, the maximal reduction in blood pressure may not occur for 2 weeks. At this time the dosage of Esidrix-Serpasil should be adjusted to the amount necessary to obtain the desired blood pressure response. For maintenance, as little as 1 tablet daily may be sufficient.

In cases of more severe hypertension, dosage of Esidrix-Serpasil can be revised upward to 4 tablets daily. When necessary, more potent antihypertensive agents such as Apresoline, Ecolid or other ganglionic blockers may be added. As Esidrix-Serpasil potentiates the action of other antihypertensive drugs, such additions to the regimen should be gradual and effects carefully observed. When Esidrix-Serpasil is started in patients already receiving ganglionic blockers, such as Ecolid, dosage of the latter should be immediately reduced by at least 50 per cent.

Side effects and cautions—As when any diuretic agent is used, patients should be carefully observed for signs of fluid and electrolyte imbalance. Esidrix in therapeutic doses is generally well tolerated. Side effects, even from large doses, have been few. Since Esidrix greatly reduces the amount of Serpasil needed, the incidence of side effects sometimes encountered with Serpasil is diminished.

Complete information on Esidrix-Serpasil available on request.

Supplied—Esidrix-Serpasil Tablets, 25 mg./0.1 mg., each containing 25 mg. of Esidrix and 0.1 mg. of Serpasil; bottles of 100.

References-1. Maronde, R. F.: Clinical Report to CIBA. 2. Greenstein, S.: Clinical Report to CIBA.

APRESOLINE® hydrochloride (hydralazine hydrochloride CIBA) ECOLID® chloride (chlorisondamine chloride CIBA)





To the relief of musculoskeletal pain, new MEDAPRIN* adds restoration of function

Analgesics offer temporary relief of musculoskeletal pain, but they merely mask pain rather than getting at its cause. New Medaprin, in addition to bringing about prompt subjective improvement, promotes the restoration of normal function by suppressing the inflammation that causes the pain.

Medaprin, Upjohn's new analgesic-steroid combination, contains aspirin plus Medrol,** the corticosteroid with the best therapeutic ratio in the steroid field.† Instead of suffering recurrent discomfort because of the "wearing off" of analgesics, the patient on Medaprin experiences a smooth, extended relief and more normal mobility.

Indications: Medaprin is indicated in mild-tomoderate rheumatic and musculoskeletal conditions, including rheumatoid arthritis, deltoid bursitis, low back pain, neuralgia, synovitis, fibromyositis, osteoarthritis, low back sprain, traumatic wrist, sciatica, and "tennis elbow."

Dosage: The recommended dosage is 1 tablet q.i.d. The usual cautions and contraindications of corticotherapy should be observed.

Supplied: In bottles of 100 and 500.

Formula: Each Medaprin tablet contains

- 300 mg. acetylsalicylic acid, for prompt relief of pain
- 1 mg. Medrol, to suppress the causative inflammation
- 200 mg. calcium carbonate, as buffer

* TRADEMARK ** TRADEMARK, REG. U. S. PAT. OFF. — METHYLPREDNISOLONE, UPJONE
TRATIO OF DESIRED EFFECTS TO UNDESIRED EFFECTS

The Upjohn Company, Kalamazoo, Michigan

Upjohn

INTRODUCING

RUBRAMIN

PURE CYANOCOBALAMIN INJECTION — CREATED AND PRODUCED

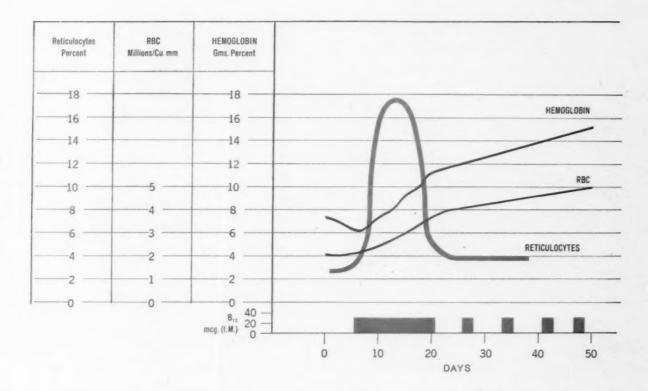
BY SQUIBB — FOR THE MOST EXACTING STANDARDS OF INTRAVENOUS,
INTRAMUSCULAR AND SUBCUTANEOUS ADMINISTRATION IN:

- · pernicious anemia
- severe nutritional macrocytic anemias
- severe nutritional neuropathies
- prevention of macrocytic anemia following partial or total gastrectomy

and for the relief of pain in such conditions as:

trigeminal neuralgia; osteoarthritis; secondary burning paresthesias; herpes zoster; and neuroblastoma in children.

RUBRAMIN PC is highly effective whenever high doses of vitamin B₁₂ are required.



TYPICAL HEMATOPOIETIC RESPONSE WHEN RUBRAMIN P C IS GIVEN INTRAMUSCULARLY TO A PATIENT WITH MEGALOBLASTIC ANEMIA (schematic)

highly potent and vital to metabolism

Vitamin B_{12} —one of the most potent biological factors known—is vital to basic metabolic functions, to normal formation of red blood cells and other formed elements of the blood, and to the functional integrity of myelinated fibers in the spinal cord and brain, as well as to the healthy condition of gastric and oral mucosa.

therapeutic agent of choice in pernicious anemia

Vitamin B_{12} is the therapeutic agent of choice in pernicious anemia, is effective in certain megaloblastic macrocytic anemias, and contributes to recovery or clinical improvement in a variety of neurological, liver and skin disorders.

non-toxic, remarkably free from side reactions

Despite its high level of activity, vitamin B_{12} is non-toxic and remarkably free from side reactions. It has been well-tolerated even when administered in massive doses.

potency confirmed by precise radioisotope measurement

The Radioisotope Tracer Method is now used routinely as an assay procedure in the production of RUBRAMIN, guaranteeing accurate label potency.

RUBRAMIN PC is now available in potencies for all your parenteral requirements: 30, 50 and 100 mcg. per cc., 10 cc. vials; 1000 mcg. per cc., 1 cc. and 10 cc. vials.





Squibb Quality—the Priceless Ingredient

RUBRAMIN'® IS A SQUIPE TRADEMARK



in epilepsy

PREREQUISITE FOR EMOTIONAL ADJUSTMENT: THERAPY

"The most effective form of psychotherapy is to demonstrate to the patient that his seizures can be adequately controlled by the use of anticonvulsant medication."1

REQUISITE FOR THERAPY: THE PARKE-DAVIS FAMILY OF ANTICONVULSANTS effective anticonvulsants for most clinical needs

bibliography: (1) Carter, S. M.: M. Clin. North America: 315 (March) 1953. (2) Chao, D. H.: Ibid., p. 465. (3) Goodman, L. S., & Gilman, A.: The Pharmacological Basis of Therapeutics, ed. 2, New York, MacMillan Company, 1955, p. 187. (4) Davidson, D. T., Jr., in Conn, H. F.: Current Therapy 1958, Philadelphia, W. B. Saunders Company, 1958, p. 568. (5) Zimmerman, F. T.: New York J. Med. 55:2338, 1955. (6) French, E. G.; Rey-Bellet, J., & Lennox, W. G.: New England J. Med. 258:892 (May 1) 1958.



FOR CONTROL OF GRAND MAL AND PSYCHOMOTOR SEIZURES DILANTIN° KAPSEALS°

"...DILANTIN Sodium is the most useful nonsedative anticonvulsant."2

"Coincident with the decrease in seizures there occurs improvement in intellectual performance. Salutary effects of the drug on personality, memory, mood, cooperativeness, emotional stability, amenability to discipline . . . are also observed, sometimes independently of seizure control." 3

The drug of choice for control of grand mal and of psychomotor seizures, DILANTIN Sodium (diphenylhydantoin sodium, Parke-Davis) is supplied in many forms including Kapseals of 0.03 Gm. and of 0.1 Gm., in bottles of 100 and 1,000.

PHELANTIN° KAPSEALS

"When it has been demonstrated that the combination of Dilantin and phenobarbital is helpful in a patient and that these drugs are well tolerated, the use of a combination capsule, PHELANTIN, is often a great morale builder because it enables the physician to reduce the total number of pills or capsules the patient is required to take. It is a cheaper form of prescription and it also prevents the patient from manipulating the dosage of his drugs."4

PHELANTIN Kapseals (Dilantin 100 mg., phenobarbital 30 mg., desoxyephedrine hydrochloride 2.5 mg.), bottles of 100.

MILONTIN° KAPSEALS • SUSPENSION

After five years of study, using MILONTIN in a series of 200 patients with petit mal epilepsy, one investigator reports: "Results confirm our previously published data on a smaller number of cases and show that MILONTIN is an effective agent for the treatment of petit mal epilepsy... relatively free from untoward side effects."5

MILONTIN Kapseals (phensuximide, Parke-Davis) 0.5 Gm., bottles of 100 and 1,000. Suspension, 250 mg. per 4 cc., 16-ounce bottles.

CELONTIN° KAPSEALS

In a recent study, 76 patients were treated with CELONTIN for periods up to two years. Included in this group were 34 patients with psychomotor seizures, 29 with petit mal, and 13 with other types. Forty per cent had marked benefit with CELONTIN (less than half their previous number of seizures), and all but 35 per cent experienced some degree of improvement. Marked benefit was obtained in 55 per cent of patients with petit mal and in 33 per cent of those having psychomotor seizures.⁶

CELONTIN Kapseals (methsuximide, Parke-Davis) 0.3 Gm., bottles of 100.

PARKE, DAVIS & COMPANY & DETROIT 32, MICHIGAN



Restore summer warmth to cold, aching extremities

R

- Increases peripheral circulation
- Relieves vasospasm

"Highly effective"* in vasospastic disorders, Ilidar promptly alleviates symptoms of cold, numb, aching extremities, with virtual freedom from unwanted side reactions. Ilidar, unlike most vasodilators, is exceptionally well tolerated: "one of the most pleasant drugs in its class to use."*

Prescribe Ilidar in peripheral vasospastic disorders to relieve aching, burning, coldness, night cramps and numbness of the extremities.

*H. D. Green and H. H. DuBose, Circulation, 10:374, 1954.

SUPPLIED: 25-mg tablets, in bottles of 100 and 500 tablets.

ILIDAR®-brand of azapetine



ROCHE LABORATORIES

Division of Hoffmann-La Roche Inc.

Nutley 10, New Jersey





SQUIBB ANNOUNCES NEW



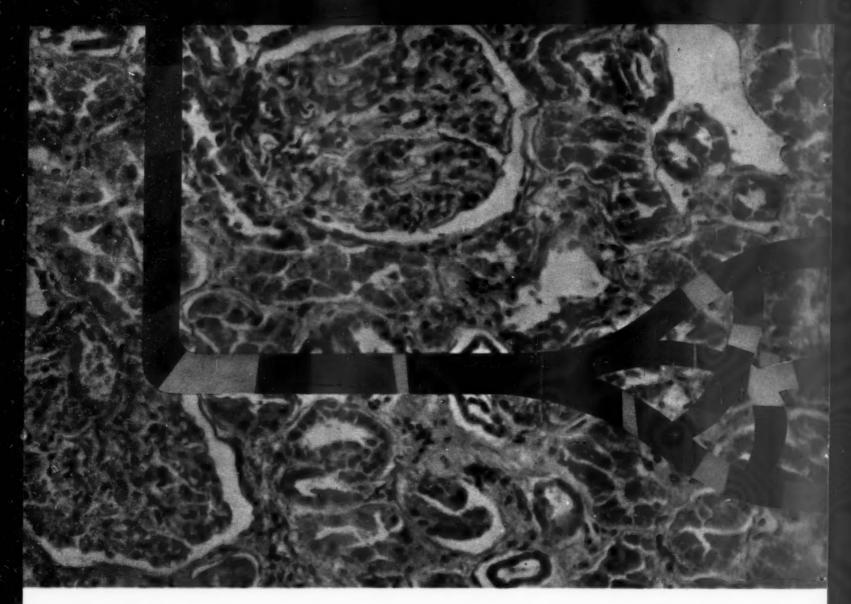
RAUTRAX

a logical combination — Raudixin enhanced by an entirely new diuretic...Flumethiazide Squibb



thus Squibb offers you greater latitude in solving the problem of

HYPERTENSION



RAUT

for the treatment of hypertension...without

Rautrax combines Raudixin with flumethiazide for control of all degrees of hypertension. Clinicians report it safely and rapidly eliminates excess extracellular sodium and water without potassium depletion. Through this dependable diuretic action of flumethiazide, the clinical and subclinical edema—so often associated with cardiovascular disease—is rapidly brought under control. 2,3,4,5 Flumethiazide also potentiates the antihypertensive action of Raudixin. By this unique dual

action, a lower dosage of each ingredient effectively maintains safe antihypertensive therapy.

Diuresis without serum electrolyte imbalance

Flumethiazide—the new, safe nonmercurial diuretic—rapidly achieves its diuretic effect without causing appreciable plasma electrolyte imbalance.^{1,2,3}
Potassium loss is less than with other nonmercurial diuretics.¹ Moreover, the inclusion of supplemental potassium chloride in Rautrax provides added protection against potassium



SQUIBB STANDARDIZED WHOLE ROOT RAUWOLFIA SERPENT FLUMETHIAZIDE POTASSIUM CHI

WHOLE ROOT RAUWOLFIA SERPENTINA

POTASSIUM CHLORIDE

fear of significant potassium depletion '2'3

and chloride depletion in the long-term management of the hypertensive patient.

Sodium and water retention is rapidly relieved,² and once the fluid balance has been brought within normal limits, continued administration of Rautrax does not appreciably alter the normal serum electrolyte pattern.

Control of hypertension with fewer side effects Raudixin—a cornerstone on which to build a therapeutic regimen for control of hypertension.

RAUTRAX... GREATER LATITUDE IN SOLVING THE PROBLEM OF HYPERTENSION

- Prompt, safe antihypertensive effect by the complementary action of Raudixin and flumethiazide
- Less potassium loss than with other nonmercurial diuretics1
- No loss in effectiveness after continued administration
- No influence on blood urea nitrogen, blood count or other hematologic values5
- Fewer and less severe side effects^{6,7}
- Less need for severe restriction in sodium intake
- Gout, purpura, or allergic reactions not reported



RAUDIXIN PLUS AN ENTIRELY NEW DIURETIC...FLUMETHIAZIDE
A NATURAL COMPANION

TO FAMOUS RAUDIXIN TO HELP SOLVE THE PROBLEM ...

HYPERTENSION

Dosage: 2 to 6 tablets daily in divided doses initially; may be adjusted within range of 1 to 6 tablets daily in divided doses. Note: In hypertensive patients already on ganglionic blocking agents, veratrum and/or hydralazine, the addition of Rautrax necessitates an immediate dosage reduction of these agents by at least 50%. A similar reduction is also necessary when these ganglionic blocking agents are added to the Rautrax regimen.

Literature available on request.

Supply: Capsule-shaped tablets each providing 50 mg. Raudixin, 400 mg. flumethiazide, and 400 mg. potassium chloride, bottles of 100.

References: 1. Moyer, J.H., and others: Am. J. Cardiol., 3:113 (Jan.) 1959. • 2. Bodi, T., and others: To be published, Am. J. Cardiol., (April) 1959. • 3. Fuchs, M., and others: Monographs on Therapy, 4:43 (April) 1959. • 4. Montero, A.C.; Rochelle, J.B., III, and Ford, R.V.: To be published. • 5. Rochelle J.B., III; Montero, A.C., and Ford, R.V.: To be published. • 6. Montero, A.C.; Rochelle, J.B., III, and Ford, R.V.: To be published. • 7. Doffermyer, L.R.; Byrd, C.W., and Lilly, W.H.: North Carolina M.J. 19:430 (Oct.) 1958.

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Squibb Quality - the Priceless Ingredient

New...for the metabolic treatment of

sulfinpyrazone GEIGY)

High Potency Uricosuric Agent

By significantly increasing renal excretion of urate and thus lowering plasma uric acid, the new highly potent uricosuric agent ANTURAN strikes directly at the basic metabolic defect in gout.

Exceptionally high potency...4 to 6 times that of probenecide...is the outstanding characteristic of ANTURAN. The effectiveness of ANTURAN is retained indefinitely and tolerance to it is good.

Clinically, Anturan:

- · Prevents formation of new tophi
- Causes gradual absorption of old tophi
- · Relieves chronic pain
- · Restores joint mobility

Anturan is not designed for the treatment of acute attacks for which Butazolidin is recommended. Detailed Information On Request

Yu, T. F.; Burns, J. J., and Gutman, A. B. Arth, & Rheumat, 1:532, 1958.

ANTURAN (Sulfinpyrazone GEIGY). Scored tablets of 100 mg, in bottles of 100.

BUTAZOLIDINE (nhenylbutazone GELGY

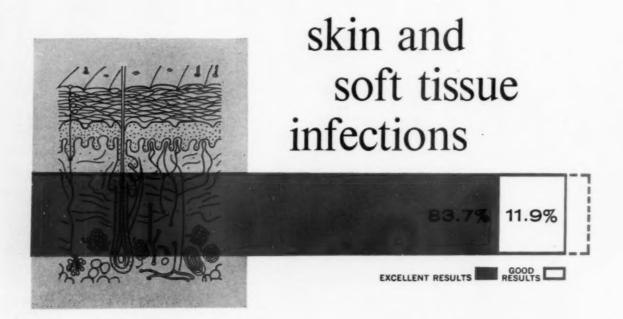
Ardsley, New York

In 259 cases of skin and soft tissue infections treated with triacetyloleandomycin, investigators¹⁻⁸ report good or excellent results in 95.6 per cent. Infections included abscesses, furuncles, carbuncles, cellulitis, infected burns, pustular acne, pyodermas, and wound infections.

Other studies, as well as wide usage, have shown that CYCLAMYCIN is also prompt and reliable therapy for respiratory and urinary tract infections due to gram-positive pathogens. CYCLAMYCIN has often proved effective against staphylococci resistant to other antibiotics.

Available in both capsule and flavored liquid form, CYCLAMYCIN is convenient to administer, readily accepted by patients of all ages.

a most effective antibiotic for



A "workhorse mycin" for common infections . . .

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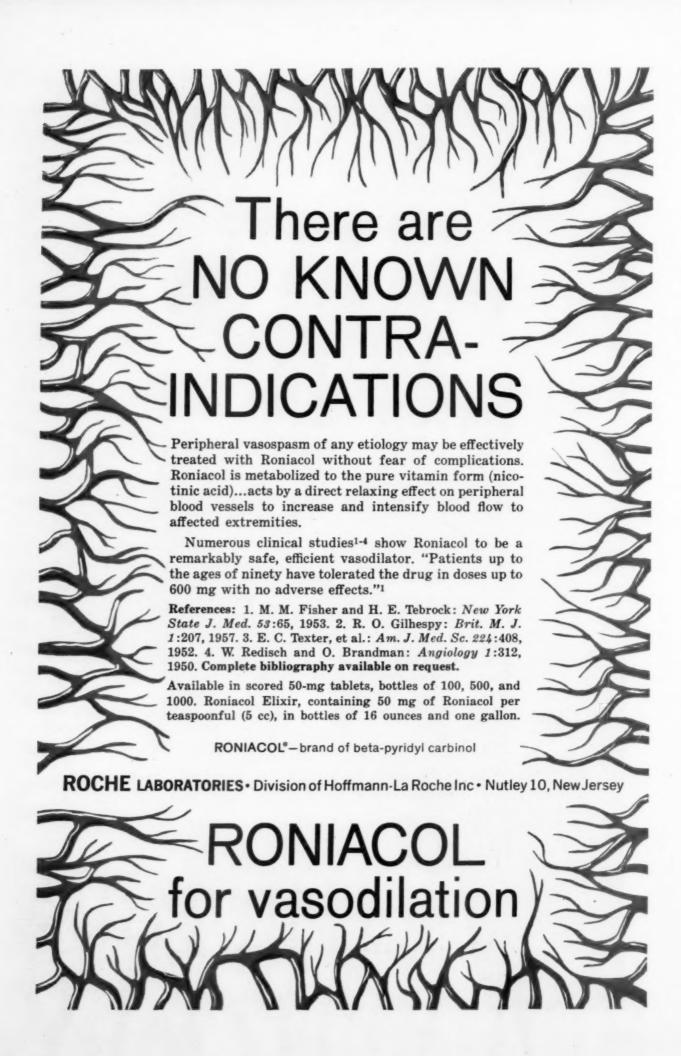
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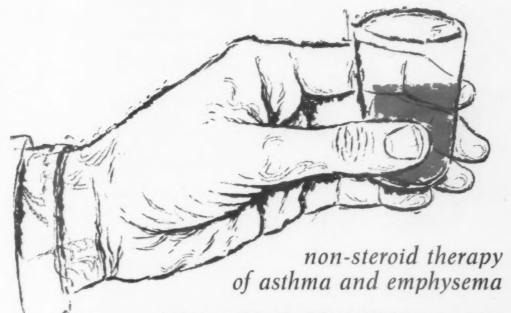
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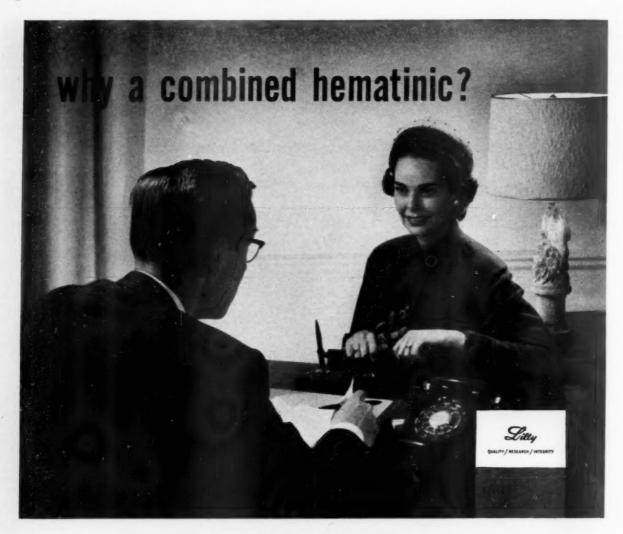
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Editorial

The Development of the Use of Iron in Hypochromic Anemia

THE history of the use of iron in hypochromic anemia is bound up with the confused concept of chlorosis; while most writers thought of chlorosis as a definite disease, anemia was spoken of largely as an incident which was usually but not always present. Sir Henry Marsh, for example, in the course of his "Remarks on Chlorosis and Haemorrhage," [1] says: "We shall not speak of chlorosis as synonymous with anaemia; the former refers to a specific disease, the latter bespeaks a state of the system either general or local . . . in chlorosis there is a change in the quality, but not necessarily a change in the quantity, of the blood; so that chlorosis must be looked upon as a peculiar and distinct disease, and not identical with anaemia . . . there is no proof of deficiency of blood in chlorosis; on the contrary, there is strong presumptive evidence that an actual excess of blood, though of inferior quality, characterizes some cases of the disease; . . . in the treatment of chlorosis, the moderate abstraction of blood by the lancet, by leeches, or by cupping, not only does not aggravate the symptoms, but, so far from this, when incidental affections demand depletion, is followed by the best effects." And further, . . . "the red corpuscles are far below the healthy standard in quantity; their appearance, however, under the microscope, is natural." Nonetheless Marsh valued iron highly in the treatment of chlorosis: "Neither do bark, nor mercury, nor wine, nor bleeding, nor opium, nor antimony . . . exhibit effects more mani-

festly therapeutic than iron does in this disease; nor does iron bring more of wealth to the inhabitants of the country from the bowels of whose earth this valuable ore is dug up, than it does of richness to the blood of the chlorotic patient. . . Whether the preparations of iron produce their effects directly by augmenting the proportion of red corpuscles in the blood, or indirectly by invigorating and improving the digestive function, still there is no medicine the curative properties of which are more fully established." The great French clinician Trousseau, like so many others, was vague and confused about the nature of chlorosis [2]. "Chlorosis should be regarded as a nervous disease causing an alteration of the blood rather than a cachexia producing nervous disorders. . . We have in the same ward a young girl of eighteen years who following strong emotion became chlorotic in four days. This shows how little importance one must attach to the original (primitif) state of the blood." Trousseau believed that there was some relation between chlorosis and menstrual trouble, but it was not purely a matter of blood loss. "Uterine hemorrhage and nose bleeds are . . . sometimes the effects rather than the causes of chlorosis. . . It is well known that chlorosis is a disorder which often recurs very easily; and I have told you that a woman who has been profoundly chlorotic for a long time retains to the end of her life traces of this serious neurosis." Trousseau thought that iron was useful in chlorosis under certain conditions

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although he did not think of it as a specific. In some cases he believed that a cure was obtained from peroxide of manganese, and he was puzzled because he thought that food always contained enough iron to supply any lack: "You will agree, gentlemen, that the interpretation is not easy for those who wish to find, in the iron prepared by the pharmacist, the element which repairs the blood." Actually Trousseau thought that iron was sometimes downright dangerous especially if there was any question of the patient having tuberculosis [3].

It was Blaud however who over a hundred years ago insisted on the value of iron in chlorosis [4]: "Preparations of iron which restore to the blood the stimulating principle which it has lost, that is to say its coloring matter, play the part of the most efficacious substances . . . but when it does not reach the blood in sufficient amount it can not restore to this fluid the principle which it has lost." He therefore recommended a specific preparation "which fulfills the essential conditions." This consisted of a mixture of sulfate of iron and subcarbonate of potassium made into pills with mucilage and taken in a certain dosage, finally reaching sixteen pills daily "whereupon a rose tint is promptly restored to the cheeks and life to the eyes. We affirm that up to the present it has never failed in our hands." Blaud definitely rated his iron pills as a specific for "chlorotic affections." Felix Niemeyer, the eminent German clinician supported Blaud's contention [5]: "If ever a medicine deserves the name of a specific then iron is a specific for chlorosis," as did Immermann [6] in his classic monograph on chlorosis. The latter states that "The exceptional effectiveness of iron in chlorosis is explained by the richer production of iron containing haemoglobin as a consequence of the use of iron . . . less intelligible is another obvious fact, that large doses of the medicine cure the disease more rapidly than small and intermittent doses."

But it was Hayem, the French hematologist [7], who first noted that in chlorosis and certain other anemias the red cells were not only small and irregular in shape but contained less coloring matter—hypochromic anemia. Hayem actually gives credit for this observation to Johann Duncan who in 1867 "we believe was the first who had the idea of studying the coloring power of the cells with the aid of salty solutions of blood. . . The interesting researches of this author in chlorosis induced him to think

that each cell contained less hemoglobin than normal." Unfortunately these observations were published in an inaccessible periodical (Beiträge zur Path. u. Therap. der Chlorosis, Sitz d. k. Akad. d. Wissensch., II Abt. April-Heft 1867). Hayem pursued the matter further [8], testing the action of iron in chlorosis: "Let us examine, for example, a case in which the red count was 5,352,000 globules. These elements, relatively numerous, were so altered as to shape and richness in hemoglobin that the blood in consequence was only feebly colored. With 5,352,000 cells it was no more colored than if it contained only 2,500,000 normal cells; so that the average value of each cell in hemoglobin was greatly reduced. When one gives a good iron preparation the number of red cells varies but little . . . while the color progressively betters. This favorable result is due to a return of the cells to their physiological state. These elements acquire normal dimensions and at the same time a quantity of coloring matter proportional to their volume." A more precise statement could hardly be made today.

But not everyone agreed that iron was a specific for chlorotic anemia. The great Virchow himself was doubtful [9]. "I shall only recall one of the most striking and at the same time accessible examples of this kind, the treatment of chlorosis with iron . . . Herr M. begins with a statement whose basis it appears to me, is wanting—to wit, that completely developed chlorosis can be cured by no remedy other than iron; nevertheless, one notes that it is precisely in many cases of advanced chlorosis that iron is not tolerated, whereas many plant remedies exert a very favorable effect."

Actually Bunge [10], the German physiological chemist, retarded the subject for years. He devoted himself to the question of whence comes the iron in hemoglobin. He was doubtful from the start about the usefulness of inorganic iron in chlorosis because "Iron is split off in the digestive canal as insoluble 'Hämatin,' and we know nothing further about its subsequent fate. Most vertebrates therefore form hemoglobin from other iron combinations." Further, he develops the syllogism: "In chlorosis the hemoglobin is diminished. After administration of inorganic iron one sees it increase. Hemoglobin is an iron compound. What more natural than the conclusion that the iron administered is used in building hemoglobin? Nevertheless this conclusion is erroneous. Newer researches

make it probable that the iron which doctors give to chlorotics to form hemoglobin is not absorbed at all." He concluded therefore that the ("organic") iron in food only was absorbed and used. But the height of his confusion was the supposition that iron therapy was successful in chlorosis because of suggestion. "Chlorosis is only a symptom of nervous or psychic disturbance which makes the patient highly suggestible." In answer to the question of why only iron and not other medicines work in chlorosis as a vehicle for suggestion he says that the doctors themselves have not had faith in other medicines and hence had no confidence in their own suggestion. "One's own confidence is notably the first requirement for the success of suggestion." This idea Bunge lifted in toto from an article by Dr. Ringier [11] in which the treatment of chlorosis by suggestion is taken up. Most of those who discussed Bunge's paper at the congress were against his views. Nevertheless, so influential was Bunge's voice that for years inorganic iron was under a cloud and if iron was used at all "organic" preparations were insisted on. Bunge's position was supported in a slightly different manner by Carl von Noorden [12], another influential German physician. Von Noorden believed that in chlorosis it was not so much lack of iron as a diminution of the growth energy of the hematopoietic organs that was at fault. "The diminished powers of the blood building organs in chlorosis need a jolt, a stimulus. Such stimuli are of many sorts; let us consider iron. . . In my judgment there is no lack of iron in the body of chlorotics but rather of growth and proliferative energy of the blood forming organs." He rated arsenic as highly as iron in therapy of chlorosis. Holding these views Von Noorden believed iron acted simply as a stimulus to blood formation and therefore was needed only in small doses; such treatment was obviously often inadequate and served to discredit iron as a therapeutic agent.

Later, in his pretentious monograph on chlorosis, Von Noorden [13] restated his views. "The disease occurs exclusively in females usually in the developmental years. The cardinal symptom is anemia. The disease develops spontaneously—at least other causes of severe anemia are absent. The anemia depends on insufficient blood formation, especially of hemoglobin, and not on increased destruction." He qualifies this statement by admitting that chlorosis occasionally occurs in males. "Chlorosis" and anemia are different

concepts. "The former designates a disease, the latter the symptom of a disease. . . Not a word is said about iron deficiency as a cause but "chlorosis is due to diminished energy of the blood forming organs."

The British, however, remained on an even keel about the question. MacCallum [14], for example, showed that inorganic iron, after feeding, could be found in the wall of the small bowel, and Stockman [15] reported carefully controlled observations in patients with chlorosis on the rise of hemoglobin after the administration of iron and the failure of other drugs such as arsenic and manganese. Osler summed it up [16] by saying, "A few weeks' administration of iron . . . usually suffice to restore a ruddy glow to the most pallid cheek."

Between questions of organic versus inorganic iron, and small versus large doses the whole subject became so confused that Williamson and Ets (The value of iron in anemia, Arch. Int. Med., 36: 333, 1925) as recently as 1925 thought they had administered the coup de grâce to iron therapy in anemia when they concluded: "Inorganic iron . . . is absorbed . . . but is not converted into hemoglobin. Animals made anemic by one or several large bleedings do not recover any more rapidly when inorganic iron is given. . . In the light of the foregoing experiments the administration of inorganic iron has no therapeutic value in anemia."

Really modern ideas about hypochromic anemia and its relation to iron defficiency began to be held in the thirties with the paper of Witts [18] on a condition which he called simple achlorhydric anemia. Witts was strongly influenced by Knud Faber who had previously associated gastric achylia and chlorotic anemia. The main features were: Occurrence usually in middle aged females, absence of free hydrochloric acid in the gastric juice, glossitis and palpable spleen (sometimes), anemia of a microcytic type with low color index. In some cases there were vague gastrointestinal symptoms and menstrual disturbances. Iron was 100 per cent effective in treatment; large doses were necessary, the equivalent of 60 gr. daily calculated as iron and ammonium citrate.

Witt's communication was followed by a torrent of confirmatory papers under various names [19-24]. The implication of most of these writings is to the effect that this syndrome is a specific disease; some authors, such as Witts, Dameshek, Mills, and Vanderhoef and Davis

have definitely stated that such is their belief.

Wintrobe and Beebe [25] reviewed the subject in monographic form and on the whole gave support to the current ideas. Bloomfield [26] however insisted that "chlorosis and idiopathic hypochromic anemia can not be differentiated into independent entities and that neither is a specific disease, but the cases represent a syndrome with many variations," with blood loss (iron deficiency) as the predominant factor.

Recent studies of the absorption, distribution, transport and use of iron in these types of anemia have at long last put the value of iron on a permanent and intelligible basis [27].

ARTHUR L. BLOOMFIELD, M.D.

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An Evaluation of Intermittent Peritoneal Lavage*

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Lt. W. C. Cooper, M.C., U.S.N., Lt. Comdr. R. H. Watten, M.C., U.S.N. §
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THE physical characteristics and suitability of the peritoneal membrane and cavity as an exchange route for substances of various molecular dimensions, as well as red and white blood cells, have been studied by a number of investigators [1-7]. During the period of World War II, as knowledge of acute and reversible forms of renal insufficiency increased, the stimulus was supplied to investigate this medium as a means of treating uremia. The careful and extensive studies of Seligman, Frank and Fine [7-9] entitle them to special recognition among the early investigators [10-20], and it was their technic of continuous peritoneal lavage which was used most frequently. This technic, however, was complex, required close supervision for prolonged periods and was attended by the dangers of inducing overhydration and/or peritonitis. These disadvantages and the advent of the artificial kidney accounted for the virtual abandonment of this particular procedure.

More recently Grollman et al. [21,22] have renewed interest in the intermittent method of peritoneal lavage. Utilizing this technic they have shown that it is possible to achieve longer survival periods in dogs following bilateral nephrectomy than have been obtained with an artificial kidney. This observation in itself means little in terms of clinical utility, for the dog is well suited for needle drainage of the peritoneal

cavity and has an intolerance for the artificial kidney not shared by other species [23]. In addition, survival periods of eighty-five, eighty-nine and ninety-seven days [24–26], which are comparable to those achieved by Grollman et al. [21] and Houck [27] in dogs, have been obtained in patients virtually devoid of renal excretory function by repeated treatments with the artificial kidney, a feat which to our knowledge has not yet been accomplished in human subjects with intermittent peritoneal lavage.

In treatment of patients with renal failure, however, the procedure appeared to carry little risk and served as an effective exchange vehicle [21]. These assets, together with the inherent simplicity and availability of the technic, suggested wide clinical applicability. Studies were therefore undertaken to evaluate the procedure within a framework of experience with renal insufficiency which included the use of the artificial kidney dating from 1950 [28–30].

MATERIAL

Eleven patients with various forms of acute or chronic renal disease were studied. At first, plastic gastric or nasal oxygen tubes in which additional holes had been cut were used; but these proved to be unsatisfactory because of obstruction due to kinking, blood clots or omentum. Several tubes superior to these have since been developed and were used in the

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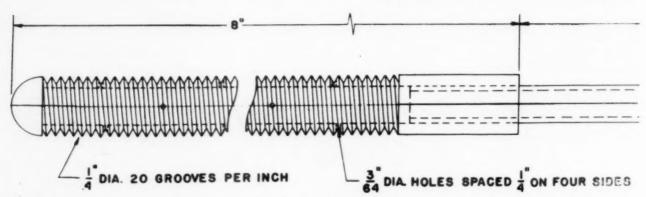


Fig. 1. Peritoneal lavage tube.

more recent cases. These tubes are made of polyvinyl chloride. One is 8 inches long, transversely ridged (outer diameter, 1/4 inch; inner diameter, 1/8 inch), in which sixty small holes have been hand-punched. (Fig. 1.)* The ridging helps to prevent kinking as well as blockage by the omentum. It will function with omentum tightly around it or in a container packed with shredded cotton and tissues. A larger tube with deeper and finer ridges is also being tested.* These new tubes may still become blocked but the blockage is due to a fibrinocellular clot which may be removed by passing a ureteral catheter or urethral catheter stylette down the lumen of the tube; thus it is not necessary to add heparin to the lavage solution. Using a ureteral catheter and knowing the length of the tube, one can determine whether or not the lumen is free throughout the entire length of the tube and the position of both can be readily ascertained radiographically.

Usually the tube was surgically inserted in the operating room in the belief that it could be placed deep in the posterior pelvis under direct vision and the incision closed tightly in layers, thus re-establishing water-tight integrity. The alternative method employed a small incision made in the midline directly below the umbilicus with insertion of the tube through a No. 22 gallbladder trocar. This procedure was performed at the bedside.

Commercial intravenous solutions, warmed in running water to which 2 ampules (100 ml.) of sodium bicarbonate have been added, were introduced through intravenous tubing, mixing occurring in the peritoneal cavity. (Table I.) Potassium chloride was added when indicated. Calcium gluconate and the water-soluble vitamins were administered parenterally. In short term dialyses and in patients with acute renal insufficiency, no magnesium was added [31]. At the end of two hours the solution was drained off into the same intravenous bottles after reinserting the airway needle through the inlet of the rubber stopper.† Drainage is usually complete within twenty

* Available from the Medical Development Corporation, Box 421-BV, Miami 37, Florida.

† Major Nestor M. Hensler, M.C., U.S.A.F., used this

to twenty-five minutes. In children proportionately smaller amounts of the standard solutions were used. When a solution of lower osmolarity is desired, a bottle of normal saline solution is substituted for the bottle of 5 per cent dextrose in saline solution. The osmolarity can be increased by adding hypertonic dextrose solution. Similarly, the sodium bicarbonate, initial pH and osmolarity can be altered by substituting varying amounts of ½6 molar sodium lactate. Many variations are possible and the resulting solutions, although failing to reconstitute exactly the extracellular fluid in electrolyte, hydrogen ion and osmolar concentrations are adequate for the intended purpose and the necessary ingredients are available in all hospitals.

The patients were given a broad-spectrum antibiotic parenterally and in a few instances terramycin or a combination of streptomycin and penicillin has been added to the dialyzing solution. The number of dialyses performed per day has varied from 1 to 10.

An accurate record of fluid balance was kept and the patients weighed daily on an in-bed scale accurate to within 50 gm. [32].

RESULTS

The measurement data and some observations on the appearance of the return fluid will be recorded first. Summaries of the clinical experience in ten of the eleven cases and the complication encountered will then be presented.

Measurement Data. The number and duration of the lavages, as well as the pertinent balance data, are summarized in Table II. In Case x, N. P. G., forty-six lavages were performed over a twenty-one-day period, the longest period of

particular technic at the Letterman Army Hospital in San Francisco. Lavages were successfully performed in three patients for periods up to eighteen days, and it was this work which provided the immediate stimulus for our studies. Major Hensler gave 1 gm. of calcium gluconate for every two lavages and felt that untoward effects of hypocalcemia were avoided.

TABLE I
SOLUTIONS USED FOR PERITONEAL DIALYSIS

Solution	Volume (ml.)	Na (mEq.)	Cl (mEq.)	HCO ₃ (mEq.)	Glucose (gm.)	рН	Osmolarity
5% Dextrose/water	1,000				50		
5% Dextrose/isotonic saline	1,000	155	155		50		
Normal isotonic saline	1,000	155	155				
NaHCO ₃ (3.75 gm./50 ml.)	100	89	* * *	89		* * *	
Total	3,100*	399	310	89	100		
Concentration per liter		128	100	28	32.5	8.0	400

^{*} Commercial solutions contain 20 to 100 ml. in excess of 1 L. The mean amount instilled is 3,180 ml.

time and the largest number of lavages accomplished with a single tube insertion. One of the new tubes which had been inserted through a trocar was used. In all, fifty-three lavages were performed in this patient, which is the greatest number for an individual. The longest period of lavage was twenty-seven days. Since at one time or another varying amounts of leakage around the tube occurred in most of the patients, the error in the fluid balance data is toward falsely low output values. The discrepancy, however, in all cases (except Case v, L. L.) in which the measured input exceeded the collected drainage, was less than 8 per cent of the input volume and despite the apparent positive fluid balance, negative weight balances were obtained in ten of the eleven cases. Appropriate adjustment of the enteral and parenteral fluids is an obvious additional measure to control the fluid balance. With these measures the complications of overhydration were avoided.

The accuracy of fluid balance data, assuming a constant policy on the part of the supervising personnel, varies considerably among patients depending upon such factors as vomiting, diarrhea, perspiration, hemorrhage and weeping lesions. The following observation was made not with the intention of inquiring into the exact fluid metabolism of patients with renal insufficiency but rather to acquire some idea as to how well fluid balance data correlated with changes in body weight in a representative group of patients with various types of severe renal insufficiency undergoing peritoneal lavage. It was believed that adequate precautions had been taken to assure judicious fluid therapy. Thirtyfive observations in five of these patients were compared with a similar number of observations

made in six other patients chosen at random, who also had severe renal insufficiency but did not receive peritoneal lavage. As it is generally accepted that changes in body water correlate well with changes in body weight over short periods of observation, the calculated change in the state of hydration arrived at from fluid balance data was plotted against the change in body weight. The correlation coefficient in the non-dialyzed group was 0.95, indicating that the change in body weight could be predicted with reasonably high precision from the fluid balance data. In the patients undergoing peritoneal lavage the correlation coefficient was 0.77, indicating unacceptably large errors in prediction based on fluid balance data. This observation leads to the conclusion that a daily body weight record is indispensable in evaluating the state of hydration in patients receiving peritoneal lavage.

The ratios of the concentration of urea nitrogen [33], * creatinine, potassium, phosphorus and uric acid [37] in the dialysate at the end of two hours and in the blood are listed in Table III. These ratios are approximate and tend to be low, for two or more dialyses were performed while usually only one blood determination was obtained each day. They are not to be interpreted as values describing equilibration curves but since the plasma values often do not change markedly in any one twenty-four-hour period, and the sampling includes a wide range, the ratios are adequate for predicting the amount of the individual substance which will be removed

^{*} Urea nitrogen accounts for 82 per cent (range 70–90) of the total nitrogen [34,35] in the lavage solution, which also contains measurable amounts of alpha-amino nitrogen [36].

TABLE II

NUMBER, DURATION AND FLUID RECOVERY DATA WITH PERITONEAL DIALYSIS—BODY WEIGHT CHANGES OVER THE PERIOD OF DIALYSIS

Case No. and Patient	Dialyses	Duration	Peri	toneal Flui	d (L.)	Body Weight (kg.)			
Case No. and Patient	(no.)	(days)	In	Out	Balance	Before	After	Change	
ı, R. W. H.	25	10	81.9	88.9	- 7.0	55.8	53.0	- 2.8	
п, S. B. I.	13	4	42.7	40.6	+ 2.1	69.7	66.6	- 3.1	
III, K. S. McK.	17	10	57.0	61.7	- 4.7	64.3	62.3	- 2.0	
IV, R. S. B.	19	6	62.6	58.7	+ 3.9			*****	
v, L. L. L.	14	4	45.8	40.5	+ 5.3	85.3	84.0	- 1.3	
vi, E. D.	10	7	32.5	34.0	- 1.5				
VII, L. W. H.	21	11	30.7	29.1	+ 1.6	27.5	29.0	+ 1.5	
viii, G. R. G.	29	12	95.6	88.6	+ 7.0	71.5	66.9	- 4.6	
ıx, M. B. C.	43	27	54.1	53.5	+ 0.6	19.1	17.8	- 1.3	
N. P. G.	7	3	22.8	21.0	+ 1.8	60.1	58.6	- 1.5	
x, N. P. G.	46	21	151.0	164.6	-13.6	62.8	52.3	-10.5	

by dialysis. The simple calculation of plasma concentration times ratio times dialysate volume equals the amount removed, a value of greater utility and significance than clearance figures.

It can also be seen from the large total amounts of urea nitrogen and potassium removed in all of the lavages performed in eight of the patients in whom these data were collected (Table IV), that this is an effective means of removal of these substances from the body.

In the last twenty-eight hemodialyses performed on the Kolff-Brigham model of an artificial kidney, the amount of urea nitrogen removed in 5.5 hours was 62.1 ± 15.8 gm. In

TABLE III

RATIO OF THE CONCENTRATION OF VARIOUS SUBSTANCES
IN THE DIALYSATE AT THE END OF TWO HOURS TO
THAT OF THE BLOOD CONCENTRATION DETERMINED
THE SAME DAY

		Ratio of Dialy- sate and Blood				
Blood	Dialy- sate	Concentration Mean and S.D.*				
41	111	0.84±0.05				
**	1	0.74 ± 0.09 0.88 ± 0.14				
11	18	0.67 ± 0.12				
15	35	0.57 ± 0.13				
	(N Blood 41 49 8 11	41 111 49 181 8 114 11 18				

^{*} Standard deviation.

two of these patients both dialytic procedures were employed. In Case IV, R. S. B., 61.5, 62.8 and 60.3 gm. of urea nitrogen were removed in three successive hemodialyses while 87.5 gm. of urea nitrogen were removed in a total of nineteen peritoneal lavages. In Case I, R. W. H., 51.3 gm. of urea nitrogen were removed in one hemodialysis and 145.5 gm. of urea nitrogen were abstracted in a total of twenty-five peritoneal lavages. Approximately ten two-hour peritoneal dialyses are required to remove as much urea nitrogen as will be accomplished with one five- to six-hour hemodialysis.

In one patient (Case VIII, G. R. G.) the dialysate was left in for a period of four hours and was then followed by another instillation for a similar period. Blood and dialysate urea nitrogen concentrations were determined in duplicate at hourly intervals. In another patient tritiated water (HTO) was administered intravenously at the time the dialysate was instilled. Urea nitrogen and HTO radioactivity* were determined in simultaneous plasma and dialysate samples. In addition to the hourly samples, ten- and twenty-minute values were also determined. In both patients the urea concentration was nearly equal in plasma and dialysate in two hours. Eighty per cent equilibration was achieved in one hour. The curve describing the equilibration of HTO indicated that equi-

* Tritium radioactivity was determined on vacuum distilled samples of water from plasma or dialysate. Radioactivity was measured by liquid scintillation counting.

TABLE IV

TOTAL AMOUNTS OF UREA NITROGEN AND POTASSIUM REMOVED IN ALL OF THE DIALYSES
PERFORMED ON INDIVIDUAL PATIENTS

C 1	Patients											
Substance	R. W. H.	R. S. B.	K. S. McK.	L. L. L.	S. B. I.	L. W. H.	G. R. G.	E. D.				
UN ₂ (gm.)	145.0	88.0	59.0	61.0 175.0	59.0	50.0 120.0	120.0	32.0 115.0				

librium with dialysate and with whole body water was equally rapid and that for purposes of water movement the dialysate represents an extension of the body water compartment as is the case for other intracavitary water such as that in the intestine and bladder. Equilibration of HTO was essentially complete at one hour and 80 per cent equilibration was achieved in less than forty minutes.

Plasma and dialysate osmolarity measurements indicate that the osmotic gradient remains in the direction of plasma to dialysate for over two hours, after which there is a slow approach to equilibrium. Consequently larger total amounts of urea and water as well as certain other diffusible substances, may be removed by a greater number of lavages of shorter duration than can be accomplished over the same interval with the standard two-hour procedure. The standard two-hour procedure ordinarily is adequate but in instances of extreme uremia and acidosis, intractable pulmonary edema or advanced potassium intoxication, the shorter periods of dialyses (circa one hour) may be resorted

In six lavages, three containing 20 units of regular insulin and three without added insulin, the glucose concentrations [38] at the end of one hour were found to be 60 and 49 per cent of the original concentration in the solution. Insulin apparently did not increase the uptake of glucose nor did it appear to have any additional influence on the serum phosphorus or potassium concentrations. It is possible, however, that some changes would have been found if the studies were continued over a longer period. In thirteen observations the glucose concentration of the dialysate at the end of two hours averaged 27.8 per cent of the control value, with a range of 18 to 42 per cent. Assuming that no significant amount of glucose is metabolized within the

peritoneal cavity, the technic is a convenient way to administer substantial amounts of calories since the patient will abstract in the order of 75 gm. of glucose from the average dialysis. The changes in blood sugar were considered appropriate and do not require special comment.

Appearance of the Return Fluid. The return fluid is usually clear and almost colorless, but it may be opalescent, yellow and opalescent or some variant ranging to grossly bloody. The protein concentrations in the non-bloody dialysates have ranged from 5 to 150 mg./100 ml. and the cell counts from 10 to 400 per cu. mm. The protein concentration is usually in the order of 50 mg./100 ml.* Opalescence is generally best correlated with the number of cells present and usually clears on centrifugation. The cells are predominantly polymorphonuclear leukocytes. In the early experience, when cloudy dialysates containing such cells were first seen there was speculation as to the significance of the finding. The following observations and information appear pertinent:

1. In twelve female mice repeated thirty-minute dialyses were attempted. In five animals more than three (three to six) dialyses were accomplished with results similar to those which have been obtained a number of times in human subjects; i.e., the fluid which originally may have been bloody would clear, or fluid which was originally clear would become opalescent

* The protein concentration was determined by adding 6 ml. of 3 per cent sulfosalicylic acid to 2 ml. of straight or diluted lavage fluid. The turbidity was measured in a Coleman spectrophotometer at 650 mµ. and the concentration determined from a standard curve prepared from the "Lab-trol" standard. Depending on the concentration in the lavage fluid, the volume and number of individual lavages, varying amounts of protein will be lost. Although significantly large amounts of protein may be removed, it is only in prolonged lavage in patients with chronic disease that replacement therapy might be required.

Table v
Peritoneal response to solutions of different osmolarity and ph

Data	Isotonic	Hypertonic	Acid	Alkaline	
White blood count/cu. mm	1013 ±390	877 ±331	655 ± 246*	607 ±250*	
	17.3± 2.7	18.1± 1.5	12.2± 2.1	13.1± 4.1	

* Significantly different from the isotonic value.

Isotonic group: a NaCl, NaHCO₃, KCl and glucose solution—315 mOsm./L.

Hypertonic group: above solution plus additional glucose-1,600 mOsm./L.

Acid group: isotonic solution with NaHCO₃ omitted, 5 per cent acetic acid added and pH adjusted with NaOH to 5.1.

Alkaline group: isotonic solution with NaOH added and pH adjusted to 9.2.

and subsequently clear dialysates would be obtained again. Since the same solution was used in all of the dialyses, no grievous peritoneal injury had apparently been inflicted.

2. Solutions of different osmolarity and pH were injected intraperitoneally (25 ml.) into four groups of female mice. The fluid was withdrawn after thirty minutes, by which time the unbuffered solutions should have approached values near those of normal peritoneal secretion [39]. Total white counts and protein determinations were performed on those specimens which were free of visible blood. Each group, with results listed in Table v, was comprised of ten mice. The white count and protein concentrations in the hypertonic, acid and alkaline groups were no higher than in the isotonic group and actually the white count and protein concentration in the acid group and the white count in the alkaline group were significantly less (p = 0.05) than the respective values in the isotonic group. These results are presented and the suggestion offered that the cellular response elicited may depend more on the chemotactic properties of the solution instilled than on the presence of morphologic or functional alterations in the peritoneal membrane.

. 3. The basis for several technics employed in collecting white cells is that these cells easily cross the peritoneal membrane [40,41].

4. The presence of polymorphonuclear leukocytes in the peritoneal cavity exerts a definite protective action against the development of peritonitis [42].

CASE REPORTS

Acute Renal Insufficiency

CASE I. R. W. H. (U.S.N.H. 277364), an eighteen year old boy, was admitted to the U. S. Naval Hospi-

tal, Oakland, with post-traumatic acute renal insufficiency. The catabolic response was intense, requiring hemodialysis on day 6. A second hemodialysis was attempted on day 9 but was unsuccessful because of failure to obtain adequate arterial blood flow. The patient was moribund: The blood urea nitrogen was 219 mg./100 ml. and potassium, 8.3 mEq./L. The electrocardiogram revealed changes associated with advanced potassium intoxication. A gastric tube was surgically inserted intraperitoneally, at which time free blood was encountered. This could have resulted from intra-abdominal injury sustained in the original accident and aggravated by the heparin administered two to three hours earlier. Additional protamine was given, and lavage instituted and continued until day 18, by which time the patient had improved dramatically. The procedure caused some discomfort and the abdomen became distended. Two days after the procedure was discontinued, the distention had progressed to adynamic ileus which responded promptly to treatment. No organisms were cultured from the dialysates. In this case the procedure was considered lifesaving.

CASE II. S. B. I. (U.S.N.H. 287521), a twenty-six year old woman, was admitted with acute renal insufficiency following abruptio placentae complicated by afibrinogenemia. On day 8 the patient had a series of convulsions, the blood urea nitrogen was 189 mg./100 ml., and hemodialysis was attempted unsuccessfully because of ubiquitous clotting of the blood within the artificial kidney which occurred in spite of the prior administration of 120 mg. of heparin.* Because of extensive hematomas in the lower abdominal wall, two nasal oxygen catheters were surgically inserted in the left upper quadrant. A transperitoneal cesarean section had been performed eight days earlier, at which time the abdomen was noted to be "full" of free blood. One of the tubes promptly became clotted

* In the five years that the artificial kidney has been actively used at this hospital, these are the only two instances wherein hemodialysis has been attempted unsuccessfully.

and kinked, but the other, with the aid of a ureteral catheter, functioned satisfactorily for four days. All of the dialysates were grossly bloody but, other than the initial ones, revealed on centrifugation "cell packs" of less than 1 per cent. No growth was obtained from cultures of the dialysates. Diuresis had begun by the fourth day of dialysis, at which time the tubes were extruded through the incision. Her further improvement was uneventful and the procedure was considered of distinct value.

CASE III. K. S. McK. (U.S.N.H. 278368), a twenty-one year old woman, was admitted with acute renal insufficiency following abruptio placentae. On day 13, the blood urea nitrogen was 132 and the creatinine 22 mg./100 ml.; the patient remained oliguric and clinical manifestations of uremia had appeared so that a gastric tube was inserted intraperitoneally and intermittent lavage begun. At first she complained of pain which occasionally radiated to the right shoulder, accompanied by diffuse abdominal tenderness, but no rigidity or rebound tenderness was present. These findings subsequently subsided and lavage was continued until day 22. Diuresis had begun on day 19; by day 25 her condition had improved substantially and the tube was removed. No organisms were cultured from the dialysate. The procedure was considered a valuable adjunct in the management of this patient.

CASE IV. R. S. B. (U.S.N.H. 263454), a twentysix year old man, was transferred to this hospital with post-traumatic acute renal insufficiency. The catabolic response was severe, with hyperkalemia requiring hemodialysis on days 9, 11 and 12. Within twentyfour hours of the third dialysis the serum potassium was 8 mEq./L. Peritoneal lavage was instituted, utilizing a gastric tube which had been surgically inserted. Nineteen dialyses were performed through day 18 and the potassium intoxication was controlled, but the blood urea nitrogen rose from 160 to 189 mg./ 100 ml. and the patient deteriorated. A dramatic clinical improvement occurred with the fourth hemodialysis on day 19. The patient eventually died because of necrotizing papillitis on day 42. A hemolytic Staphylococcus aureas and Escherichia coli had each been cultured on one occasion from the dialysate. Upon examination at autopsy the peritoneal cavity was free of fluid and the peritoneum was smooth with no evidence of peritonitis or adhesions. The procedure was of value in controlling potassium intoxication but at the rate used it was not sufficient to prevent progression of the uremia, and dramatic improvement followed a subsequent hemodialysis.

Case v. L. L. (U.S.N.H. 285327), a sixty-one year old man, was admitted with acute renal insufficiency following a suprapubic prostatectomy complicated by the development of a bleeding tendency.

The uremia progressed rapidly and by day 6 the blood urea nitrogen was 209 mg./100 ml. and the serum potassium, 7.9 mEq./L. Peritoneal lavage was instituted rather than hemodialysis because of various arrhythmias which had been present since admission: interference dissociation, supraventricular tachycardia and ventricular tachycardia and ventricular flutter. Employing a plastic nasal oxygen tube, lavages were performed over a four-day period during which nine one-hour and five two-hour dialyses were carried out. The first tube did not work and it was necessary to insert a second one. The blood urea nitrogen and serum potassium concentrations were stabilized but the patient deteriorated. On three occasions a Pseudomonas organism, once accompanied by E. coli, was cultured from the dialysate. While preparations for hemodialysis were being made on day 10, the patient died. On examination at autopsy two loops of intestine covered with a small amount of fibrinopurulent exudate, were found to be loosely adherent to the tube directly upon entrance into the peritoneal cavity. The remainder of the peritoneum was smooth and revealed no evidence of peritonitis. More difficulty was encountered with the procedure in this patient than in any other, due largely to his confused and excited state with complete lack of cooperation. The peritoneal lavages stabilized the blood chemical findings but did not prevent further clinical deterioration.

Acute Glomerulonephritis

CASE VI. E. D. (U.S.N.H. 261804), a twentyseven year old woman, was admitted to this hospital with acute glomerulonephritis complicated by pulmonary edema, oliguria and hyperkalemia. The hyperkalemia, 7.6 mEq./L., was controlled by resins but no improvement in the pulmonary edema was achieved in several days of medical therapy. The patient was extremely obese and attempts to insert a gastric tube intraperitoneally with a trocar were unsuccessful, so this was accomplished under direct vision. Ten dialyses were performed over a seven-day period with distinct clinical improvement: the blood urea nitrogen fell from 121 to 95 mg./100 ml. and the carbon dioxide rose from 11.2 to 17.1 mEq./L. The pulmonary edema cleared. Although the measured negative fluid balance obtained by peritoneal dialysis was a modest 1,535 ml., it did not include a considerable amount of fluid lost by leakage; therefore the negative balance, without doubt, was substantially greater. Unfortunately, it was not possible to weigh the patient. This was the first patient in whom we employed peritoneal lavage and when she complained of abdominal pain and cloudy fluid was returned the procedure was discontinued. Culture of this specimen failed to grow any bacteria and our subsequent experience has indicated that cloudy return fluid does not mean that the procedure must be abandoned. Fortunately, this patient continued to improve and

was eventually discharged from the hospital free of uremia and edema but with persistently abnormal urinary findings. Peritoneal lavage was considered to be a distinct value in tiding the patient over a critical episode.

CASE VII. L. W. H. (U.S.N.H. 279344), an eight year old boy, was admitted with acute glomerulonephritis complicated by uremia, oliguria, anemia and jaundice. A plastic nasal oxygen tube was inserted surgically three days after admission, when the blood urea nitrogen was 247 mg./100 ml. This tube was kinked and another had to be inserted which functioned reasonably well for a ten-day period although marked leakage around the tube started during a severe convulsion and continued throughout the survival period. Abdominal distention and vomiting developed, and were controlled by constant gastric suction. One of the cultures of the dialysate was reported as "doubtful"; the rest were negative. Although the convulsions were controlled with parenteral Dilantin® and phenobarbital, the patient did not improve and thirteen days after admission he died. Peristalses were audible on the day prior to death. Examination at autopsy confirmed the diagnosis of acute glomerulonephritis but in addition disclosed an acute fibrinous peritonitis. In this case the procedure was considered injurious.

Chronic Renal Insufficiency

Case viii. G. R. G. (U.S.N.H. 284710), a twenty year old man with chronic pyelonephritis and uremia, had been leading an active life until two weeks prior to admission when "flu" with vomiting and diarrhea developed. The uremia became markedly worse and was complicated by a hypertensive encephalopathy. Peritoneal lavage, using a plastic gastric tube, was instituted (blood urea nitrogen 257 mg./100 ml.) and continued over a twelve-day period, but because of inadequate flow a second tube was surgically inserted through an incision in the left upper quadrant of the abdomen. Two dialysates grew out hemolytic staphylococci and one a paracolon bacillus, but the four cultured subsequent to the last positive one were all negative. Penicillin and streptomycin, and then chloramphenicol and Albamycin® were administered parenterally. During the period that dialysis was performed the patient complained of some abdominal pain and became distended. Two days after the procedure was discontinued, a dehiscence through the left upper quadrant incision occurred. Examination at autopsy confirmed the primary diagnosis; the combined weight of the kidneys was 90 gm. and there was no evidence of peritonitis. There was a loose adhesion at the site of the incision. The blood urea nitrogen was reduced to a low of 97 mg./100 ml. during the period of intermittent peritoneal lavage and it was considered that the patient had received a satisfactory therapeutic trial.

CASE IX. M. B. C. (U.S.N.H. 282627), * an eight year old girl, in whom a diagnosis of nephrosis had been made at the age of eighteen months, was admitted. From then until five years of age the patient was almost continuously edematous and at times monthly paracenteses were required. One month prior to admission she had a convulsion and the nonprotein nitrogen was reported to be 40 mg./100 ml. Other than that her condition was considered improved until one week prior to admission, when the patient contracted an acute gastroenteritis. Subsequently she became oliguric; pulmonary edema and a pericardial friction rub appeared and when the blood urea nitrogen was 180 mg./100 ml., peritoneal lavage was instituted in the hope that some reversible element existed. A total of forty-three dialyses were performed over a twenty-seven-day period. Two surgical incisions and four different plastic tubes were required to accomplish all of these dialyses. On several occasions dialysis was withheld for a day or two and the patient was hydrated in an attempt to achieve large urine volumes, but the oliguria persisted. The pulmonary edema cleared and her general condition greatly improved with dialysis. Two weeks after the procedure was discontinued the patient died, the terminal episode consisting of fever, pulmonary edema and convulsions. At autopsy the peritoneal cavity was "filled to overflowing with slightly opalescent yellowish fluid" and the parietal layer was said to have "a slightly more dense or whitish appearance than usual. The surfaces, however, are generally smooth and shiny." On microscopic examination there was fibrous thickening of the visceral peritoneum. In areas there was a moderately thick, somewhat dense layer of collagenous tissue with minimal to moderate numbers of small mononuclear cells and macrophages. The combined weight of the kidneys was 23.5 gm. and the pathologic diagnosis was chronic glomerulonephritis. Prolonged peritoneal dialysis in this patient involved a calculated risk because of the underlying nephrosis. Peritonitis was never clinically or bacteriologically (twelve cultures) evident, however; and in view of the chronic ascites, multiple paracenteses and terminal fever, it is difficult to interpret the fibrous thickening of the peritoneum detected on microscopic examination. It was considered that the procedure had been of benefit and provided the patient with an adequate therapeutic trial.

CASE X. N. P. G. (U.S.N.H. 286437), a twenty-three year old man, was admitted with bilateral hydronephrosis, pyelonephritis and uremia. When the blood urea nitrogen reached 149 mg./100 ml. one of the transversely ridged peritoneal tubes was surgically inserted through a right lower quadrant incision

*We are grateful to Drs. Earl Kolb and Karl A. Palmer of the Travis Air Force Base Hospital for making their records and the complete autopsy protocol available to us.

and seven lavages were performed over a three-day period. The procedure was extremely painful, lavage fluid extravasated into the subcutaneous tissues extending all the way up to the right axilla, and the procedure had to be discontinued. It had accomplished little and caused a great deal of pain.

On catheter drainage the patient at first improved slightly but then stabilized for a period of several weeks, after which he gradually became edematous, more uremic (blood creatinine 25 mg./100 ml.) and then pulmonary edema developed. After thirty-six hours of medical therapy the pulmonary edema had not improved and peritoneal lavage was again instituted. This time one of the transversely ridged tubes was inserted in the midline through a trocar, and in a twelve-hour period 3,390 ml. of fluid was abstracted, with a 3.9 kg. loss in body weight and definite improvement in the pulmonary edema. Twenty-eight additional lavages were performed over the subsequent eight days during which time the generalized edema cleared. Over this nine-day period the patient lost a total of 10.2 kg. and the creatinine was reduced to 15.9 mg./100 ml. Bilateral nephrostomy drainage was accomplished that day. Postoperatively, the urine volumes varied between 100 to 400 ml./day and he once again became progressively more uremic, this time complicated by an elevation of the serum potassium. The hyperkalemia was controlled by a polystyrene sulfonated resin in the sodium cycle. The lavage tube had been left in place and after eight days, during which no lavages were performed, the procedure was started again. Ten additional lavages were performed over a four-day period; the tube functioned well. The patient, however, now complained of severe pain and although peristalsis was audible, the abdomen was definitely more tender with rebound and the return fluid from the last three lavages showed a large number of white blood cells (1,140 to 2,800/cu. mm.); two of these three samples revealed organisms on Gram stain. Of the last nine specimens of return fluid which were cultured, a Psuedomonas organism was isolated from three, Aerobacter aerogenes from two, and four were negative.

It was concluded that the patient had peritonitis and the procedure was discontinued. He was started on oral neomycin therapy, parenteral antibiotics were continued, and within several days the abdominal signs cleared. The patient died thirty days later, and on postmortem examination the peritoneum had a normal appearance and there was no evidence of peritonitis.

This case demonstrates that when the new tubes are used the facility with which the lavages are accomplished depends primarily on the successful insertion of the tube within the peritoneal cavity. It should be noted that during the second series of lavages the tube was clamped off for a period of eight days, after which it still functioned well. The procedure effected a dramatic clearing of the pulmonary and generalized

edema. In retrospect it was believed that perhaps we had been somewhat too energetic and had induced a state of mild dehydration although the patient withstood the surgical procedure well. The preoperative improvement in blood chemical findings was comparable to those obtained with an artificial kidney.

COMPLICATIONS

The most troublesome complication was obstruction of the peritoneal tube. Since the majority of the tubes were inserted through incisions which the surgeon had attempted to make water-tight, this necessitated another operation. The only adhesions which have been seen have formed at the laparotomy site which, together with the bleeding tendency associated with uremia, are additional reasons for confining the surgical procedure to minor dimensions. Because of the frequent occurrence of distention, it is preferable to insert the tube below the level of the umbilicus since dehiscence is more likely to occur through higher incisions. These problems have been avoided with the use of the newly developed tubes and the occasional assistance of a ureteral catheter or urethral catheter stylet to free any fibrin clots that may have formed.* The best and simplest way of inserting the tube is by means of a small infraumbilical midline incision to the peritoneum with puncture of the membrane and introduction of the tube through a trocar. The tissue is then secured snugly around the tube to prevent leakage. This method is essentially the same as that originally recommended by Grollman and we have now returned to it as the simplest and most satisfactory. If difficulty is experienced in puncturing the peritoneum it should be either incised or the peritoneal cavity distended with several liters of dialyzing solution, as recommended by Legrain and Merrill [43], to minimize the danger of perforating the bowel with the sharp trocar. The insertion, as outlined, can be accomplished as a bedside procedure. If the tube cannot be placed in the midline it is inserted surgically in the operating room through as small an incision as the surgeon will consent to.

The procedure was attempted in an additional patient who died in the operating room. While the operation was in progress the tube was tested. The solution ran in satisfactorily but after 1,500 ml. of return fluid had been obtained the

^{*} One may choose to use two tubes as an additional safeguard but our present policy is to use only one.

With the measures outlined the serious complications of peritonitis should be avoided. Although the chances for the development of peritonitis are undoubtedly less the shorter the duration of lavage, the risk does not appear serious enough to justify the repeated removal and reinsertion of the lavage tube [43].

A prevalent opinion is that peritoneal lavage is contraindicated after "recent" abdominal surgery [14,44,49,50]. Such statements require qualification, for the earlier technic of continuous lavage was instituted immediately after rather major procedures [8] and treatment in one of our patients was started seven days after a transperitoneal cesarian section had been performed. Furthermore, it is the infrequent instance wherein any form of dialytic therapy need be instituted on the day of surgery or in the immediate postoperative period. Peritoneal lavage may be contraindicated in some patients in whom acute renal insufficiency develops following wounds [51,52] or other forms of abdominal trauma as well as in certain patients who have undergone extensive visceral or vascular surgery but the decision must be made after thorough consideration of the individual case. Even in such patients a therapeutic trial may be justified, for the risk is small.

COMMENTS

Intermittent peritoneal lavage is an effective means of treating the clinical and chemical manifestations of uremia. It can be performed in children as easily as in adults. It accomplishes its task at a significantly slower rate than the artificial kidney and this may represent a serious limitation of the technic in those patients who exhibit an intense catabolic response. More intermittent lavages will have to be performed in such a group before this point is settled but there is no doubt that the procedure is more than adequate for the majority of cases. In assisting patients with chronic renal insufficiency over acute episodes, this slower rate may have a particular suitability since the current concept of one of the leading centers employing an artificial kidney is to effect a more gradual chemical re-equilibration in such patients [53].

The procedure is an effective means of treating potassium intoxication and lends itself more readily than the artificial kidney to the management of those patients who rapidly re-intoxicate. The sodium polystyrene resins, however, appear to be so effective in controlling hyperkalemia

and potassium intoxication [54] that the indications for dialytic therapy may be reduced to those patients in whom the associated uremic syndrome demands such measures.

The medical therapy of the oliguric patient with severe pulmonary edema is extremely difficult and not infrequently ineffective. The Kolff-Brigham model of the artificial kidney has, in our experience, little to offer in such therapy although other types of artificial kidneys which also ultrafilter are capable of removing fluid at extremely rapid rates, 500 to 1,200 ml./hour [55-57]. The slower rates of fluid removal accomplished in our patients were adequate and in each case the pulmonary edema cleared. Others have similarly observed clearing of pulmonary and generalized edema with peritoneal lavage [22,49,58-60]. In this connection it might be mentioned that in one patient (Case x, N. P. G.) a state of mild dehydration was induced by removal of an excessive amount of fluid, and in both peritoneal lavage [8,15] and ultrafiltration [55] care must be taken to avoid too rapid a rate of fluid removal.

Salicylates can be recovered in the peritoneal fluid of animals [2,61] and a significant amount was present in the lavage fluid of one of these patients (Case IX, M. B. C.) following oral administration. It should be possible to recover other drugs in varying amounts, depending upon their diffusion characteristics. Although no comparative studies have been performed, it seems unlikely that the rate of removal of aspirin, certain barbiturates, bromides or thiocyanate by intermittent peritoneal lavage would approach the rates which have been obtained with the artificial kidney [62-67]. Mention might also be made of the potential value of the procedure in instances of severe hypernatremia [68-70] and its proved value in experimental studies involving small animals [71].

In conclusion, intermittent peritoneal lavage possesses important advantages of simplicity and availability. The major difficulty is the uncertainty of the outflow tract, an uncertainty that is reduced by the use of a newly developed lavage tube. The artificial kidney remains the treatment of choice, for it is faster, more reliable and, if used under ideal circumstances requires a smaller total investment of time on the part of the professional personnel than that required for adequate supervision of prolonged lavage therapy. The practical disadvantage of the artificial kidney is that the over-all requirements for

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drainage abruptly stopped. The patient died a few moments later and no further manipulation was attempted. At autopsy the tube was free but the patient had such extensive omental adhesions it seemed unlikely that satisfactory lavages could have been performed. It is in such a situation that there is also the real danger of perforating the bowel on insertion of a trocar [44].

Usually the lavage was accomplished with the patient experiencing no more than a sense of fullness or mild discomfort. Occasionally a patient complained of pain which at times was severe. Such severe pain seemed related to over-distention of the peritoneal cavity, the presence of peritonitis or the extravasation of fluid into the tissues. With the older tubes, protrusion of omentum into the tube occurred and any manipulation or movement of the tube caused pain. In the absence of some such complication the procedure was not painful and no local analgesics were added to the lavage solution.

Abdominal distention was not considered an important complication. The procedure may be associated with distention but assertions that the two are causally related may be unjustified since this complication occurs so frequently in patients with severe renal insufficiency, particularly that of the acute reversible type.

The most serious complication was the isolation of bacteria from the dialysate in five of the patients, and the development of fibrinopurulent peritonitis in an additional patient (Case vii. L. W. H.) in whom only one "questionable" culture had been obtained. These findings were not entirely unexpected. Some leakage occurred at one time or another in most of the patients so that bacteria had free access to the peritoneal cavity. The patients with chronic renal insufficiency were allowed to eat and no antimicrobials were given to sterilize the gastrointestinal tract. The irrigating solution is usually hypertonic and some transmural migration of bacteria most certainly occurs [45]. No strict aseptic technic was enforced, cultures were not obtained on each lavage, and no attempt was made to culture anaerobic organisms. The incidence of contamination of the lavage fluid may therefore have been substantially higher than the present results indicate. That bacteria can be cultured from the return fluid without the inevitable development of peritonitis is neither surprising nor original, for similar observations were made by Frank, Seligman and Fine [9] and by Odel, Ferris and Power [14]. Another observation made by the

Beth Israel group which bears repetition is that peritonitis may develop in the absence of the classic signs. These same investigators pointed out that there was less peritoneal contamination with short term or discontinuous irrigation, a view shared by all investigators [20,21,43,44]. The possibility exists, however, and adequate precautions and therapeutic measures must be taken. The current policy is to culture every third dialysate, to obtain frequent Gram stains, and to have all responsible personnel wash thoroughly or wear gloves when instilling solutions. The proximal end of the lavage tube should be kept plugged with intravenous tubing at all times, and when a new lavage is to be instilled the area of connection should be thoroughly cleansed. Most of the patients are receiving antimicrobials when the procedure is instituted and these are continued. If organisms are seen or cultured or the number of white cells greatly increased, the studies are immediately repeated.

Emphasis is thus laid primarily on early detection, and antimicrobials have not been added to the lavage solution as a prophylactic measure. If definite bacteriologic evidence or overt signs of peritonitis develop, Terramycin® or penicillin and streptomycin are added to the next lavage after which the procedure is discontinued. These measures have appeared to be adequate. For this reason and because of the coexistent renal disease and serious reactions which have accompanied the intraperitoneal use of large amounts of neomycin [46,47], such therapy has not been employed. In response to our request for his opinion on the management of peritoneal contamination and peritonitis, Dr. Jacob Fine has called attention to the likelihood of contamination by other members of the intestinal flora including Bacteroides and recommended that oral neomycin be started prior to the institution of lavage. If unequivocal contamination occurs despite this prophylactic measure, the procedure should be discontinued and appropriate antimicrobial therapy initiated via the intraperitoneal route. Dr. Fine has re-emphasized the advantages of intraperitoneal neomycin therapy in amounts not exceeding 250 mg./dose or 750 to 1,000 mg./day for several days. In unanesthetized patients the dangers of neomycin are considerably less [48]. It is planned to continue the high calorie, low protein, no milk diet in patients with chronic renal insufficiency taking oral neomycin.

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With the measures outlined the serious complications of peritonitis should be avoided. Although the chances for the development of peritonitis are undoubtedly less the shorter the duration of lavage, the risk does not appear serious enough to justify the repeated removal and reinsertion of the lavage tube [43].

A prevalent opinion is that peritoneal lavage is contraindicated after "recent" abdominal surgery [14,44,49,50]. Such statements require qualification, for the earlier technic of continuous lavage was instituted immediately after rather major procedures [8] and treatment in one of our patients was started seven days after a transperitoneal cesarian section had been performed. Furthermore, it is the infrequent instance wherein any form of dialytic therapy need be instituted on the day of surgery or in the immediate postoperative period. Peritoneal lavage may be contraindicated in some patients in whom acute renal insufficiency develops following wounds [51,52] or other forms of abdominal trauma as well as in certain patients who have undergone extensive visceral or vascular surgery but the decision must be made after thorough consideration of the individual case. Even in such patients a therapeutic trial may be justified, for the risk is small.

COMMENTS

Intermittent peritoneal lavage is an effective means of treating the clinical and chemical manifestations of uremia. It can be performed in children as easily as in adults. It accomplishes its task at a significantly slower rate than the artificial kidney and this may represent a serious limitation of the technic in those patients who exhibit an intense catabolic response. More intermittent lavages will have to be performed in such a group before this point is settled but there is no doubt that the procedure is more than adequate for the majority of cases. In assisting patients with chronic renal insufficiency over acute episodes, this slower rate may have a particular suitability since the current concept of one of the leading centers employing an artificial kidney is to effect a more gradual chemical re-equilibration in such patients [53].

The procedure is an effective means of treating potassium intoxication and lends itself more readily than the artificial kidney to the management of those patients who rapidly re-intoxicate. The sodium polystyrene resins, however, appear to be so effective in controlling hyperkalemia

and potassium intoxication [54] that the indications for dialytic therapy may be reduced to those patients in whom the associated uremic syndrome demands such measures.

The medical therapy of the oliguric patient with severe pulmonary edema is extremely difficult and not infrequently ineffective. The Kolff-Brigham model of the artificial kidney has, in our experience, little to offer in such therapy although other types of artificial kidneys which also ultrafilter are capable of removing fluid at extremely rapid rates, 500 to 1,200 ml./hour [55-57]. The slower rates of fluid removal accomplished in our patients were adequate and in each case the pulmonary edema cleared. Others have similarly observed clearing of pulmonary and generalized edema with peritoneal lavage [22,49,58-60]. In this connection it might be mentioned that in one patient (Case x, N. P. G.) a state of mild dehydration was induced by removal of an excessive amount of fluid, and in both peritoneal lavage [8,15] and ultrafiltration [55] care must be taken to avoid too rapid a rate of fluid removal.

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In conclusion, intermittent peritoneal lavage possesses important advantages of simplicity and availability. The major difficulty is the uncertainty of the outflow tract, an uncertainty that is reduced by the use of a newly developed lavage tube. The artificial kidney remains the treatment of choice, for it is faster, more reliable and, if used under ideal circumstances requires a smaller total investment of time on the part of

the professional personnel than that required for adequate supervision of prolonged lavage therapy. The practical disadvantage of the artificial kidney is that the over-all requirements for

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optimal utilization are such as to restrict its use to a comparatively few institutions. The two technics should not be thought of in exclusive terms; both are effective and the desirability of having more than one therapeutic modality available is obvious. The physician in charge continues to be the most important factor; not the dialytic technic.

SUMMARY

The use of intermittent peritoneal lavage in ten patients, for periods varying from three to twenty-seven days, is described. The smallest number of lavages performed in an individual patient was ten and the largest, fifty-three. The lavage solution is prepared simply by infusing 1 L. each of 5 per cent dextrose in saline solution, 5 per cent dextrose in water, and normal saline solution to which 2 ampules of sodium bicarbonate have been added. The solutions are available in all hospitals. Mixing occurs within the peritoneal cavity and after a two-hour period the lavage solution is drained off through the same tube used for instillation. A new intraperitoneal tube has been developed which does not kink or become obstructed by the omentum and thus greatly improves the reliability of the procedure.

In one patient with advanced uremia and potassium intoxication and in two patients with refractory pulmonary edema the procedure was considered life-saving. In all of the patients it proved to be a simple and effective means of ameliorating the clinical and biochemical manifestations of uremia. Overhydration was not observed, and if due precaution is taken in the fluid balance program this complication can be avoided.

The most troublesome complication was obstruction of the plastic tubes used in the early experience. This problem has been minimized by the use of the newly developed peritoneal tubes. The lavage is usually accomplished with the patient experiencing no more than a sense of fullness or mild discomfort. Occasionally a patient complained of pain. Severe pain may be caused by overdistention of the peritoneal cavity, extravasation of fluid into the tissues, or the presence of peritonitis.

The most serious complication was the development of peritonitis in one patient. In five of the other patients organisms were isolated from the lavage fluid; contamination, therefore, appears to be more frequent than is generally

appreciated. The presence of bacteria does not indicate the inevitable development of peritonitis, however; and with due precautions this serious complication should be avoided.

In general terms, the artificial kidney is much faster and intermittent peritoneal lavage is much simpler. Both procedures are clinically effective and the desirability of having more than one therapeutic modality available is obvious.

Acknowledgment: The constructive suggestions of Drs. J. P. Merrill, W. J. Kolff, H. A. Harper and J. Fine are gratefully acknowledged.

ADDENDUM

An idealized solution has been made available to us by Dr. Morton H. Maxwell and was used in some of the more recent cases. This solution further increased the simplicity of the procedure, particularly when used in children or in other situations wherein smaller volumes are instilled. The newly developed intraperitoneal tube has proved to be satisfactory in six other patients.

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Metabolic Alterations During Hemodialysis with the Disposable Coil Artificial Kidney*

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TALYSIS with the disposable coil artificial kidney [1] effects rapid reversal of certain metabolic alterations accompanying the uremic syndrome, including hyponatremia, hypochloremia, hypocalcemia, hyperpotassemia, acidosis, overhydration, dehydration, or combinations of these abnormalities [2,3]; in addition, other more poorly defined metabolic abnormalities which must play an important role are probably effected. By accomplishing these objectives hemodialysis has proved to be of therapeutic value in the management of the uremic syndrome. Its success is limited, however, to reversible renal lesions, since removal of abnormal metabolites cannot ultimately substitute for damaged nephrons. Those patients who can be "tided over" a temporary period of renal decompensation are the best candidates. In general, the selection of patients for hemodialysis must be individualized.

On a long-term basis, the application of basic principles of fluid and electrolyte balance and judicious use of symptomatic measures can produce gratifying results in patients with the uremic syndrome. Reduction in morbidity and prolongation of productive life are possible through meticulous attention to details of management [4]. In certain instances of advanced uremia, however, it may be necessary to accomplish rapid correction of the metabolic alterations. In chronic renal disease and in certain instances in acute renal failure, the use of the artificial kidney has reduced morbidity and mortality [5].

During the procedure, electrolyte concentra-

tions and total body fluid volume can be changed rapidly. In some patients, these changes may be hazardous. The hazards include digitalis intoxication induced by electrolyte alteration [6,7,\\$8] and additional renal impairment produced by dehydration or congestive heart failure. To minimize these dangers, some investigators have used short dialysis periods [9].

This report reviews the alterations observed during fifty hemodialyses with the disposable coil artificial kidney, correlates some of these changes with time of dialysis, and defines the nature of the electrolyte, urea and fluid changes.

MATERIALS AND METHODS

Fifty dialyses with a disposable twin coil artificial kidney [1] were performed in patients with acute and chronic renal disease. With this equipment it was possible to maintain blood flow through the dialysis coils at an average rate of 300 cc., with variations from 200 to 400 cc. per minute. In most instances the procedure lasted six hours, in several eight to ten hours, and in one twelve hours. The composition of the dialysis bath is shown in Table 1. Concentrations of potassium in the bath were varied according to the initial plasma level and the clinical evidence of potassium intoxication.

Simultaneous blood specimens were drawn from the patient (A specimens) and from the tubing returning blood to the patient from the dialyzing unit (V specimens). Such specimens were drawn at the start of dialysis and every two hours during the procedure. Plasma was separated at once and frozen for

§ Electrocardiographic evidence of digitalis intoxication has now been observed in nine of thirty dialyses in patients receiving digitalis, an incidence of 30 per cent.

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TABLE 1
COMPOSITION OF THE DIALYSIS BATH

Compone	nt (gm./100 L.)	Na ⁺ (mEq./L.)	K ⁺ (mEq./L.)	Ca ⁺⁺ (mEq./L.)	Mg ⁺⁺ (mEq./L.)	Cl- (mEq./L.)	HCO ₃ - (mEq./L.)
NaCl	570 =	97				97	* *
NaHCO ₃	300 =	36					36
KCl	40 =		5			5	
CaCl ₂	28 =			5		5	* *
$MgCl_2$	15 =				3	3	
Total		133	5	5	3	110	36

Note: Sugar 0.4%, lactic acid to adjust pH to 7.4. Concentrations may be varied depending on clinical situation.

later analysis. The values for sodium, chloride, potassium, carbon dioxide combining power and osmolality were determined. In most patients, blood urea nitrogen values, blood volumes, hematocrits and weights were recorded before and after dialysis. In selected patients, serum calcium and phosphorus were measured.

The dialysis bath was changed every two hours. Aliquots of the bath (D specimens) were taken at the beginning and end of each period. Concentrations of sodium, chloride, potassium and osmolality were determined in these samples.

Sodium and potassium concentrations were determined with a flame photometer using a lithium internal standard. Chlorides were determined by the method of Schales and Schales as modified by Summerson. Venous plasma pH was measured in a Cambridge Research pH meter. Osmolality was determined in a Fiske Osmometer. Plasma volumes were estimated by the dye dilution technique using T-1824.

RESULTS AND DISCUSSION

Blood Urea Nitrogen. The initial blood urea nitrogen levels ranged from 50 to 345 mg. per cent. In most patients it was above 100 mg. per cent. No urea was added to the dialysis bath. In the thirty-seven patients in whom values were available after dialysis, the blood urea nitrogen had been lowered by 16 to 237 mg. per cent; the average change was a decrease of 81 mg. per cent, (Table II.) Serial determinations in nine patients are presented in Figure 1. The final blood urea nitrogen values in these nine patients ranged from 28 to 158 mg. per cent, and for the entire series, from 23 to 158 mg. per cent.

Plasma and Red Blood Cell Volume. Change in plasma volume and red blood cell mass was determined by measurement of blood volume, arterial hematocrit and body weight before and

after dialysis. Each patient received 500 to 2,000 cc. of whole blood during dialysis. Some patients also received isotonic saline solution in amounts up to 2,000 cc. during the procedure.

Blood volume results, available in twenty-eight patients, are recorded in Figure 2. In nineteen of these patients the plasma volume was expanded by more than 400 cc. prior to dialysis, in nine it was within normal limits. After dialysis the plasma volume was reduced by 400 cc. or more in nineteen patients, but of these, plasma volume had previously been within normal limits in four. There was no change in plasma volume in seven patients.

Red blood cell volume was decreased initially in twenty patients and was normal in eight. In eleven patients the red cell volume, which had been low initially, increased by 200 cc. or more after dialysis. There were no significant changes during dialysis in fourteen patients. Three patients, one of whom had an initially low value, showed a fall in measured red cell volume greater than 200 cc.

All but two of these same twenty-eight patients showed a rise in hematocrit during dialysis. The average change was plus 6 per cent. The rise in some instances represented an absolute increase in red blood cell mass from transfusion; in others it was a relative increase due to decrease in plasma volume; in some, both factors were present. The fall in hematocrit in the two patients previously mentioned was slight. Both of these patients received only 500 cc. of whole blood during the procedure, and in only one was there a concomitant fall in red cell volume.

The changes in weight (water) following dialysis are shown in Table II. Only three of forty patients gained weight. The remainder lost

Table II
ELECTROLYTES AT THE START AND END OF DIALYSIS

	K (mEq.		Na (mEq.		CI (mEq.		HC (mM		Osmol	ality	BU (mg.		Ca (mg.		P (mg. %)		Weight Change
Patient	before	after	before	after	before	after	before	after	before	after	before	after	before	after	before	after	(kg.)
1	6.5	5.0	138	143	103	92	8.5	11.7	368	301	134	118					
2	5.3	5.9	140	144	93	113	12.6	25.1	298	295	78	30	5.5	10.6	4.5	4.6	-2.7
3	4.4	4.5	132	147	83	112	31.3	23.8	332	307	150	92	0.7	0.0	10.4	5.4	
4	3.3	3.3	134	146	93	107	4.9	18.1	345	345	156	72	9.7	9.0	5.8		-4.5
5	7.4	4.9	138	144	100	106	10.8	22.3	369	315	247	60	8.4		3.0		
6	5.5	3.7	120	138	81	103	15.8	18.6	291	293	104	25					-1.8
7	5.9	3.8	133	143	95	105	15.3	23.0	306	300	80	23					-0.9
8	7.2	4.4	126	134	93	103	9.4	17.6	342	311		111					-1.1
9	4.2	4.3	139	144	98	108	15.4	25.6	344	313	150						-1.3
10	3.0	3.3	130	132	83	96	24.2	25.3	315	303	153						
11	5.6	4.6	124	136	96	106	16.6	17.8	303	294	100	33					-1.3
12	7.5	4.3	109	127	82	98	7.4	19.0	275	280	95	54					
13	4.7	3.9	128	134	92	103	13.6	18.9	292	285	101	56					-3.
14	4.0	3.5	142	140	108	108	9.5	21.2	341	305	138	95					-2.
15	5.5	3.9	136	138	80	105	11.8	22.5	370	313	234	75	****			* * * *	
16	5.7	3.4	138	140	86	107	9.4	19.9	418	316	200		7.4				-0.
17	5.7		129				24.0				50	***	5.6			****	1.1
18	4.5	4.1	130	137	108	106	13.2	23.1	322	292	125	46	6.8		9.3		+1.
19	6.4	3.4	146	142	108	110	9.0		390	350	188	80	7.4		15.9		-2.
20	6.1	4.3	133	137	107	101	3.2	14.2	343	296	174	138					
21	4.6	3.7	141	139	82	99	13.4	15.5	408	344	234						-0.
22	5.1	4.4	147	144	100	106	14.3	21.3	391	325	228						
23	4.3	4.5	134	142	98	106	11.8	18.5	342	321	150	69	8.9	11.8	9.5	6.9	-0. -7.
24	3.2	4.7	129	144	80	106	19.8	18.5	331	308	180	23	7.8	12.5	16.0	9.5	-5.
25	7.7	4.7	123	135	78	98	7.6	18.4	338	320	159	100	9.0	9.1		13.3	3.
26	7.4	3.0	129	138	104	108	8.4	20.3	332	300	127	57					-0.
27	7.4	4.1	134	138	108	108	11.7	21.8	308	300	88	31			1	4.4	-2.
28	6.1	4.1	128	142	95	110	15.4	23.4	310	303	109	47	8.4	8.8	4.4	4.4	-0.
29	4.7	3.7	131	141	94	108	11.7	18.5	335	297	260	36	9.7	9.6	6.8	3.7 9.7	-0.
30	4.0	3.8	134	137	87	101	14.6	18.8	349	321	345	108	7.4	9.5	13.3	7.7	-0.
31	6.3	3.7	150	148	109	109	18.7	22.2	385	334	105	63					-1.
32	6.5	2.3	105	128	80	92	4.0	9.0	405	329	210	112	5.4		19.8	7 7	+1.
33	4.7	4.5	125	136	93	104	17.8	22.1	326	320	122	70	8.1	9.8	10.5	7.7	
34	5.3	3.9	128	142	94	105	5.8	17.6	369	324	315	158	8.2		19.6		-2.
35	4.6	4.0	126	134	84	97	10.6	18.3	322	315	184	80					-
26	4.9	3.5	125	128	109	108	0.9	3.5	323	301	201						-0
36 37	4.4	4.1	138	138	81	96	17.0	20.4	368	304	194	122					-0 -1
38	3.9	3.2	114	132	85	99	4.3	20.3	255	274	1111						-2
39	4.0	4.5	132	143	98	107	14.8	22.5	312	304	122	36					+0
40	4.0	4.2	126	137	95	105	14.5	18.8	325	305	134	62					-
44	7.5	4.4	125	126	89	95	10.9	16.2	315	299	180	120					-2
41	4.3	4.7	139	137	92	106	12.3	19.0		305							-2
43	5.5	3.4	139	141	88	95	22.2	29.6		330		122					-1 -0
44	5.1	4.8		152		103	30.5	28.4		330			10.0	10.0	10 4	15.6	-2
45	5.7	2.9	122	132		102	7.2	13.7	385	310	112	89	10.0	10.0	19.4	15.0	
44	4.5	4.3	134	138	96	104	14.2	17.2	325	307	124	72					-1
46	4.5	3.7		139		107	14.9	22.8		303	95	25					-1
47 48	3.4	4.9		128		96	14.0	18.0		337		85					-0
49	5.2	3.2		139		97	11.5	16.7		326		131					-1
50	5.0	4.5		140		99	18.5	21.8	350	321		+ * *	****			****	***

from 0.2 to 7.0 kg. The average change was a loss of 1.7 kg.

Thus far we have no effective formula for predicting fluid requirements during dialysis. It is obvious that overhydration can be corrected and that transfusion for anemia can be under-

taken with little risk of congestive heart failure during dialysis. During dialysis ultrafiltration takes place, due to the osmotic and hydrostatic pressure differences across the dialysis membrane. The latter is a function of the rate of flow and resistance in the system. Excessive dehydra-

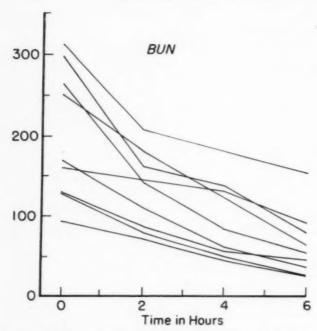


Fig. 1. Changes in blood urea nitrogen (mg. per cent) during dialysis in nine patients.

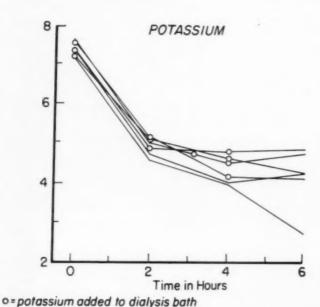


Fig. 3. Changes in plasma potassium (mEq./L.) during dialysis in six patients with marked hyperpotassemia.

tion during dialysis should be avoided since the resultant circulatory change may cause further renal impairment.

Changing water balance during dialysis may be estimated by frequent weight determinations on a bed scale, serial hematocrits, and measurement of pressure in the system by a mercury manometer attached to a sidearm in the tubing distal to the dialysis coils.

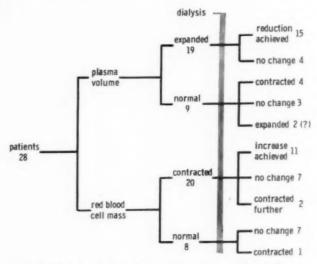


Fig. 2. Blood volume changes in twenty-eight dialyses.

Electrolytes. The electrolyte changes in all patients are presented in Table II. Hyponatremia, hypochloremia, hyperpotassemia, hyperosmolality and acidosis were frequently present prior to dialysis. In general, all measured electrolyte abnormalities tended to be corrected during the procedure. Detailed analysis of the changes in electrolytes follows.

Potassium: The range of plasma concentrations prior to dialysis was 3.0 to 7.7 mEq./L. In twenty-one patients the initial plasma potassium was elevated above 5.5 mEq./L.

Since potassium diffuses rapidly across the cellular membrane during dialysis, plasma and bath concentrations changed very quickly toward equilibrium; in all instances the major change took place in the first two hours. A graph showing the change over a six-hour period in six patients with severe hyperpotassemia is presented in Figure 3. In four patients in the series additional specimens were obtained fifteen, twenty-five, twenty-seven and sixty minutes, respectively, after the start of dialysis. In each case the plasma concentration had already been lowered by 0.7 to 1.2 mEq./L. Subsequent lowering of plasma levels was less, even with continued omission of potassium from the bath. At the end of dialysis the plasma potassium concentrations ranged from 2.3 to 5.9 mEq./L. Only two patients had values below 3.0 mEq./L. and only one patient had a value above 5.0 mEq./L. In the two patients with low values, 2.3 and 2.9 mEq./L., the plasma potassium concentration rose and, within twenty-four hours after dialysis, the values were 4.1 and 4.4 mEq./L. Both patients had acute renal

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failure secondary to septic abortion. The rapid rise in plasma potassium was probably due to tissue breakdown.

Initial specimens of blood returning to the patient from the coils (V specimens) had low potassium concentrations, around 1.0 mEq./L. in most instances. As expected, addition of potassium to the bath at any time immediately increased the potassium concentration in the V specimens.

Concentrations of potassium in the dialysis bath, representing potassium removed from the patient, were very low unless supplementary potassium had been added. However, small increments in concentration during each dialysis period reflect large withdrawals of potassium from the patient because the total bath volume is 100 L. For example, a rise in bath concentration of only 1 mEq./L. represents a total removal of 100 mEq. from the patient.

These changes are illustrated in Case 31, Table III. The patient's plasma potassium concentration (A specimens) was lowered by 2.6 mEq./L. (initial concentration, 6.3 mEq./L.; final concentration, 3.7 mEq./L.) during dialvsis, the greatest change occurring in the first two hours. The lower concentrations in the blood after passage through the coils (V specimens) reflect the loss of potassium into the dialysis fluid. A gradual increase in the potassium content of the bath specimens occurred during each twohour period. Early in the final period, 20.0 gm. (2.4 mEq./L.) of potassium chloride were added to the bath. In consequence the final V specimens and the final D specimens were increased by approximately 2.4 mEq./L.

In Case 31 the extracted potassium in the bath amounted to 240 mEq. in the six hours of dialysis. On the basis of plasma volume and weight, this patient's extracellular volume was estimated to be approximately 13 L. With a plasma potassium change of 2.6 mEq./L. during dialysis, approximately 35 mEq. of potassium should have been removed if extracellular ion sources alone were affected. Therefore roughly 200 mEq. must have been removed from sources other than extracellular fluid. This pattern of potassium loss was observed in eighteen patients. It is assumed that concentrations of extracellular and bath ions move toward equilibrium, depending exclusively upon the exchange gradients across the coil membrane. The concentration of extracellular potassium, however, depends to some degree upon exchange gradients across the

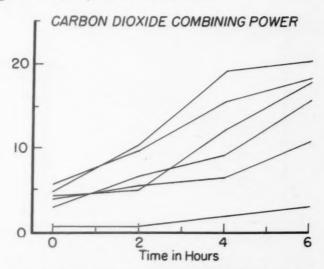


Fig. 4. Changes in plasma carbon dioxide combining power (mM./L.) during dialysis in six patients with marked acidosis.

cellular membranes. Early in dialysis, elevated plasma potassium concentration results in a steep gradient toward the dialysis bath.

Bicarbonate: The carbon dioxide combining power prior to dialysis ranged from 0.9 to 31.2 mM./L. Some degree of acidosis was pres-

ent in forty-five patients.

The plasma bicarbonate tended to rise during dialysis, but more slowly than other ions, possibly reflecting in part concomitant correction of intracellular deficits and neutralization of fixed acids. A graph is presented in Figure 4 showing the change during six hours of dialysis in six patients with severe acidosis. In one patient, severely acidotic at the start of dialysis, the carbon dioxide combining power rose from 0.9 to only 3.5 mM./L. with relief of symptomatic acidosis. The carbon dioxide combining power in the remainder of the patients in the series ranged from 9.0 to 29.6 mM./L. after dialysis. In two patients, however, the plasma pH values after dialysis were 7.46 and 7.45 at a time when the carbon dioxide combining powers were 13.7 and 16.7 mM./L., respectively. The normal pH value in the setting of low bicarbonate levels reflects an adequate respiratory compensation for acidosis.

The progressive rise in plasma bicarbonate during dialysis was reflected in the carbon dioxide combining power of the blood returning to the patient from the coils. V values were always slightly higher than corresponding A values. This is illustrated in Case 31. (Table III.)

Sodium and chloride: Plasma sodium concentrations prior to dialysis ranged from 105 to 150

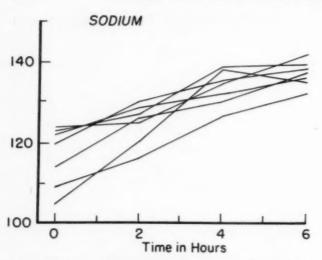


Fig. 5. Changes in plasma sodium concentration (mEq./L.) during dialysis in seven patients with marked hyponatremia.

mEq./L. In nine patients the concentration was less than 125 mEq./L.

During dialysis, the plasma sodium rose toward normal levels, most of the rise occurring in the first four hours. This change in plasma sodium is illustrated in Figure 5 in which the alterations during six hours of dialysis are

TABLE III
ELECTROLYTE CONCENTRATIONS IN A, V AND BATH
SPECIMENS DURING DIALYSIS IN A
REPRESENTATIVE PATIENT

	10110				
	K (mEq./ L.)	Na (mEq./ L.)	Cl (mEq./ L.)	HCOs (mM./L.)	Osmol
		A Specimo	ens		
Start	6.3	150	109	18.7	385
2 hours	4.6	148	108	17.6	351
4 hours	4.0	148	108	20.6	335
6 hours	3.7	148	109	22.2	334
		V Specimo	ens		
Start	1.2	143	102	20.5	322
2 hours	1.3	152	110	21.8	330
4 hours	1.2	145	102	23.3	310
6 hours	3.5	150	110	25.1	322
		D Specime	ens		
First bath					
Start	0.0	138	107		283
End	0.9	138	108		294
Second bath					
Start	0.1	151	117		304
End	0.8	150	115		308
Third bath					
Start*	0.1	138	106		288
End	3.3	145	115		310

^{* 20} gm. KCl added to bath just after this specimen.

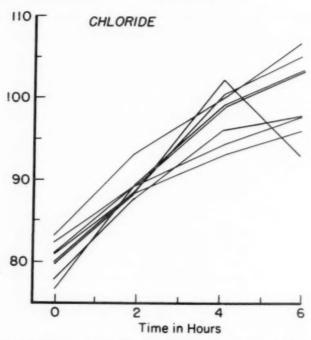


Fig. 6. Changes in plasma chloride concentration (mEq./L.) during dialysis in eight patients with marked hypochloremia.

presented in seven patients with marked hyponatremia.

After dialysis plasma sodium concentrations ranged from 126 to 152 mEq./L. One patient had a concentration over 150 mEq./L. and only four patients had concentrations lower than 130 mEq./L.

The range of plasma chloride concentration prior to dialysis was 77 to 109 mEq./L. In twenty-eight patients it was less than 95 mEq./L. The pattern of change during dialysis was similar to that of sodium. (Fig. 6.) After dialysis the plasma concentrations ranged from 92 to 113 mEq./L.

Calcium and phosphorus: To judge from the limited data in our series, dialysis appears to correct existing abnormalities in the levels of both calcium and phosphorus.

Osmolality: The plasma osmolality prior to dialysis ranged from 255 to 418 mOsm./L. These were distributed as follows: less than 300, six patients; 300 to 325, twelve patients; 326 to 350, fifteen patients, 351 to 375, eight patients; 376 to 400, five patients; over 400, three patients. The osmolality fell progressively during dialysis in those instances with initial elevation, mainly due to the clearance of urea. Again, the greatest change occurred early in the procedure in most cases. The changes during six hours of dialysis are outlined in Figure 7 for eight patients with

marked hyperosmolality. Throughout dialysis, the osmolality of the V specimens remained relatively constant at a lower level than that of the A specimen. Rise in osmolality of the bath could be demonstrated in most instances and was less pronounced in the later periods of dialysis. These changes are also demonstrated in Case 31. (Table III.)

COMMENTS

These data illustrate the magnitude of change in body water, electrolytes and urea during dialysis with the artificial kidney. From the data presented in this report it is apparent that hemodialysis results in partial or complete correction of extracellular fluid and electrolyte abnormalities. Others [2,9] have observed reduction in elevated levels of sulfates, phosphates and uric acid during dialysis. It is reasonable to assume that metabolic abnormalities not reflected in these measurements are also altered by hemodialysis.

Overhydration may be corrected during dialysis. Although this effect may be used to advantage in certain clinical situations such as congestive heart failure, there is danger of excessive removal of fluid. Some patients have been depleted of as much as 7.0 kg. of fluid during dialysis for six hours; subsequent prolonged oliguria was attributed to circulatory changes and reduction in renal blood flow.

Electrolyte correction is achieved as the plasma is brought into equilibrium with a dialysis fluid of appropriate electrolyte composition. The rapidity of change in plasma concentration depends on gradients across the coil and cellular membranes. Therefore if one ion such as potassium is omitted from the dialysis bath, the plasma-to-bath gradient will be steep and rapid exchange will proceed. From the data presented, it is obvious that exchange is effected from intracellular as well as extracellular ion stores. It is possible to achieve correction of intravascular fluid ion concentration in two to three hours by appropriate prescription of bath composition and by frequent bath changes. Additional advantages may be obtained from longer periods of dialysis as the result of alteration of intracellular electrolyte abnormalities and removal of other undefined metabolites contributing to the uremic syndrome.

In our experience six hours appears to be the optimal duration of dialysis, and no additional

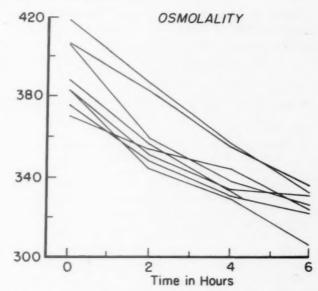


Fig. 7. Changes in plasma osmolality (mOsm./L.) during dialysis in eight patients with marked hyperosmolality.

clinical benefit has been noted in patients treated with dialysis for longer periods of time.

SUMMARY

The electrolyte, urea and fluid changes in uremic patients during fifty dialyses are reviewed.

Hemodialysis with the artificial kidney is a useful procedure in the correction of various electrolyte and fluid abnormalities in the uremic syndrome. Dialysis may achieve striking electrolyte concentration and fluid volume correction in a period of a few hours; additional correction or depletion of intracellular ion concentration may be accomplished by dialysis for longer periods.

Overhydration may be corrected during hemodialysis, but excessive dehydration may be induced and this can cause further renal impairment.

Dialysis for six hours with bath changes every two hours appears to be the optimal procedure.

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The Effect of Chlorothiazide on Renal Excretion of Electrolytes and Free Water*

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CHLOROTHIAZIDE (6-chloro-7-sulfamyl-1,2,4 benzothiadiazine-1,1-dioxide) is an orally effective sulfonamide which promotes the renal excretion of chloride, sodium and potassium [1]. The compound has been found to be at least as potent as organic mercurial agents in inducing diuresis in patients with congestive heart failure, hepatic cirrhosis and nephrosis [2–4].

A number of clinical observations have suggested that chlorothiazide differs from other diuretic agents in its mode of action on the renal tubule [2]. In an attempt to characterize these differences the drug was compared with a mercurial diuretic (meralluride) in respect to effects on reabsorption of electrolytes and excretion of free water.

According to current concepts, sodium and/or chloride reabsorption occurs both in the proximal and distal tubule [5]. Solute reabsorption is isosmotic in the proximal tubule and may or may not be isosmotic in the distal tubule. In the presence of antidiuretic hormone, back diffusion of water is thought to be facilitated in the distal tubule. In the absence of antidiuretic hormone (water diuresis), the solutes are considered to be selectively reabsorbed, leaving the osmotically non-obligated water for excretion as so-called free water (CH,O) [6]. Accordingly, information may be obtained concerning the site of action of a diuretic within the renal tubule by determining its effect on the excretion of free water. Thus, if sodium and/or chloride reabsorption is inhibited in the proximal tubule, the solutes may be excreted either isosmotically or may become available for more distal (selective) reabsorption, leading to increased excretion of free water; whereas inhibition of sodium and/or chloride reabsorption in the distal tubule may be expected to result in reduced excretion of free

Meralluride has been shown to increase the excretion of free water [7], an observation best explained by inhibition of electrolyte reabsorption in the proximal tubule. The data to be presented demonstrate that chlorothiazide either does not change or decreases the excretion of free water despite a marked increase in solute clearance. The results suggest that chlorothiazide inhibits electrolyte reabsorption in both the proximal and the distal tubule.

It has been shown previously that protracted administration of chlorothiazide may be associated with hyperuricemia [2]. In an effort to determine whether or not the rise in serum uric acid might be due to impaired renal excretion of uric acid, the uric acid clearance also was determined in the present study before and after administration of chlorothiazide.

METHODS AND MATERIALS

Nineteen studies were performed in fifteen patients who gave no evidence of cardiovascular or renal disease. The subjects at the time of study were in the postabsorptive state. Each study included: (1) The establishment of water diuresis, induced a half hour before the study by oral administration of \pm 1,000 ml. water and subsequently maintained throughout the experiment with 5 per cent dextrose in water given intravenously at a rate of 17 to 20 ml./minute. (2) Two to three control periods of ten minutes each to determine baseline values for urine flow, glomerular filtration, free water and solute clearance, and electrolyte excretion during water diuresis. (3) Similar measurements after the intravenous administration of either 2 ml. meralluride† or 250 to 500 mg. chlorothiazide.

† Meralluride U.S.P. contains 0.13 gm. of organic mercurial per milliliter, equivalent to 39 mg. Hg. In addition, each milliliter contains 48 mg. of theophylline.

^{*} From the Department of Medicine of the Presbyterian Hospital, the Francis Delafield Hospital in the City of New York, and the College of Physicians and Surgeons of Columbia University, New York, New York. Supported by a grant from the U. S. Public Health Service and the Fleitas Fund.

(4) In some instances induction of an osmotic diuresis by administration of 4.7 per cent mannitol in water, infused at a rate of 22 ml./minute, to increase the urine flow and the non-reabsorbable solute load.

For the determination of active water reabsorptive capacity (T_{H2O}), the subject was deprived of water for eighteen hours prior to the study. Antidiuresis was assured by the intravenous administration of Pitressin® 100 mU./kg. body weight and by an infusion of hypertonic (10 per cent) mannitol solution.

Inulin for measurement of glomerular filtration rate was added to the infusion fluid after an adequate priming dose to maintain the plasma level at 25 mg. per cent. Renal plasma flow was measured with paraaminohippuric acid [8]. Blood samples were obtained at appropriate time intervals; urine was collected by an indwelling catheter, and the bladder was emptied by means of air.

Plasma and urine samples were analyzed for inulin by either Schreiner's modification of the Roe method [9] or a modification of the diphenylamine method [10]; for sodium and potassium by an internal standard flame photometer; for chloride by potentiometric titration [11]; for uric acid by ultraviolet absorption according to the method of Praetorius [12]; and for total solute content by freezing point depression with a Johlin freezing apparatus and a bridge null-point detector unit of Bowman [13].

Calculations. The free water clearance (C_{H2O}) is defined [6] as the osmotically not obligated water excreted during water diuresis and calculated as:

$$C_{H_{2}O} = V - \frac{U_{OSM}V}{P_{OSM}}$$
, where V represents the urine

flow in milliliters per minute, and $U_{\rm OSM}$ and $P_{\rm OSM}$ represent the solute concentration of urine and plasma in milliosmols per kilogram of water. During anti-diuresis the value for the free water clearance is negative and is thought to reflect the amount of water actively reabsorbed in the collecting ducts. This negative value is defined as $T_{\rm HaO}^{\rm o}$ [14].

RESULTS

The results are summarized in Tables I and II and in Figures 1 through 5. In the tables and figures the effects of 500 mg. of chlorothiazide and of 2 ml. of meralluride are compared.

Effect on Glomerular Filtration, Renal Plasma Flow and Arterial Blood Pressure. In all eleven experiments the administration of chlorothiazide was followed by a prompt, sustained decrease in glomerular filtration rate. The average reduction was 16.9 per cent with a range of 7.8 to 30 per cent. The renal plasma flow was measured in two patients. In one subject (patient 7) a drop of 10 per cent was noted, in the other (patient 6) a 6 per cent increase was observed;

these changes in renal plasma flow appear insignificant, but further studies are necessary. The arterial blood pressure was followed in three patients throughout the clearance studies using a conventional cuff manometer. No change in arterial pressure was observed.

Meralluride administration was followed by an average increase in glomerular filtration rate of 5 per cent. The changes noted were inconsistent (Table 1), and in general did not appear to exceed the error of the method.

Effect on Urate Clearance. In the course of the foregoing studies chlorothiazide (six patients) in contrast to meralluride (three patients) produced a significant increase in uric acid clearance. These observations are being investigated further and will be reported in detail at a later date.

Effect on Plasma Electrolyte and Total Solute Content. The experimental protocol required the administration of large amounts of fluid in order to establish and maintain a water diuresis. The average initial solute content of the plasma was 285 mOsm./L. (range 273 to 304 mOsm./L.). During water diuresis the solute content decreased to an average value of 282 mOsm./L. (range 269 to 295 mOsm./L.). Administration of chlorothiazide was followed by a further decrease to 276 mOsm./L. (range 244 to 296 mOsm./L.), whereas administration of meralluride was followed by no further change in plasma solute content (mean value 283 mOsm./L.; range 269 to 296 mOsm./L.). The greater average reduction in plasma solute content of 6 mOsm./L. following administration of chlorothiazide was of doubtful significance. However, in certain patients the reduction in plasma osmolality after chlorothiazide was striking. The concentrations of sodium and chloride in the plasma paralleled those observed for total solute.

Effect on Renal Excretion of Sodium, Chloride and Potassium. The marked difference between chlorothiazide and meralluride in their effects on sodium and chloride reabsorption is illustrated by the increased rejection of filtered sodium ($C_{Na}/C_{IN} \times 100$) or filtered chloride ($C_{Cl}/C_{IN} \times 100$) and consequent increased sodium ($U_{Na}V$) and chloride ($U_{Cl}V$) excretion. (Table 1.) Chloride excretion after administration of meralluride was measured in only three patients since the effect is well established.

The excretion of potassium increased an average of threefold after administration of chloro-

TABLE I

EFFECT OF CHLOROTHIAZIDE AND MERALLURIDE ON SOLUTE, ELECTROLYTE AND WATER EXCRETION (The clearances of inulin, total solute, "free water," sodium and chloride have been corrected to 1.73m² body surface area.)

Case (No.)	Age (yr.)	Sex	S.A. (m²)	Protocol*	V (ml./ min.)	CIN (ml./ min.)	Cosm (ml./ min.)	CH2O (ml./ min.)	C _{H2O} /C _{IN} (%)	UosmV (µOSM./ min.)	U _{Na} V (µEq./ min.)	UCIV (µEq./ min.)	UKV (µEq./ min.)	C _{Na} (ml./ min.)	C _{C1} (ml./ min.)	C _{Na} /C _{IN} (%)	C _{Cl} /C _{IN} (%)
1	20	M	1.80	C	24.9	136	6.4	17.5	12.9	1903	275	259	46				****
				Ct.	28.8	111	13.0	14.7	13.2	3846	1264	1063	206				
2	53	M	1.82	C	17.3	115	7.3	9.4	8.2	2019	202	202	75	1.5	2.2	1.3	1.9
				Ct.	18.7	80	10.6	8.0	10.0	3109	801	682	96	6.3	7.1	7.9	8.9
3	64	M	1.86	C	12.0	88	3.2	7.9	9.0	950	86	73	26	.7	.7	.8	.8
				Ct.	16.7	77	7.7	7.8	10.1	2230	739	691	85	5.5	6.3	7.1	8.2
4		M	1.92	C	14.7	104	4.7	8.6	8.3	1460	193	241	70	1.4	2.4	1.3	2.3
				Ct.	19.7	85	9.5	8.3	9.8	3004	850	948	361	6.9	8.8	8.1	10.4
5	36	M	1.75	C	25.5	147	6.0	19.1	12.9	1635	191	165	111	1.5	1.7	1.0	1.1
				Ct.	31.6	129	14.0	17.2	13.3	4040	1520	1065	221	11.8	11.2	9.2	8.8
				Ma.†	24.9	101	9.5	15.3	15.1	2680	1230	899	160	9.8	9.2	9.7	9.1
6	46	M	1.77	C	15.6	128	3.6	11.6	9.1	1078	126	105	23	.9	1.1	.7	.8
				Ct.	23.4	107	10.8	12.1	11.3	3176	1270	922	216	9.3	9.5	8.7	8.8
71	35	F	1.81	C	10.9	110	2.0	8.4	7.6	621	162	120	28	1.1	1.1	1.0	1.0
. 4				Ct.	20.6	93	10.2	9.6	10.3	3080	1341	1158	80	9.3	10.9	10.0	11.7
8	29	F	1.54	C	22.8	161	9.0	17.6	10.9	2015	461			4.1		2.5	
-	-			Hg	31.9	159	14.3	21.6	13.6	3330	904			7.9		4.9	
9	22	M	1.64	C	20.1	134	5.7	15.3	11.4	1483	160			1.3		1.0	
				Hg	25.8	133	7.3	20.0	15.0	1862	431			3.4		2.5	****
10	31	M	1.73	C	19.6	121	6.3	13.3	11.0	1826	313			2.3		1.9	
				Hg	31.0	134	10.9	20.1	15.0	3205	760			5.7		4.3	
11	46	M	1.84	C	21.7	122	4.9	15.5	12.7	1403	303			2.2		1.8	
-				Hg	30.5	144	6.4	22.3	15.5	1860	529			3.8		2.6	
12	41	M	1.83	C	12.7	103	4.0	8.0	7.8	1240	220			1.6		1.5	
-				Hg	20.2	112	6.2	12.8	11.4	1649	485			3.4		3.1	
13	61	M	1.73	C	9.4	81	5.7	3.7	4.6	1672	308			2.6		3.2	
				Hg	19.1	83	9.2	9.9	11.9	2734	707			5.6		6.8	
6	46	M	1.77	C	19.1	154	3.4	15.2	9.9	971	143	114	29	1.1		.7	
-				Ct.	25.9	130	10.4	14.9	11.4	3055	1134	878	141	8.6		6.6	
				C	16.9	157	4.0	12.5	8.0	1149	160	160	34	1.1	1.7	.7	1.1
				Hg	26.3	166	7.1	21.0	12.6	2047	394	365	26	2.9	3.8	1.8	2.3
14	52	M	2.12	C	11.2	90	1.9	7.3	8.1	690	123	107	61	.7	.7	.8	1.0
				Ct.	16.4	83	8.9	5.5	6.6	2823	1157	788	176	7.6	7.1	9.2	8.5
				Ma.†	19.0	71	10.5	5.0	7.0	3168	1010	768	119	6.7	7.2	9.4	10.1
				C	10.2	105	2.0	6.4	6.1	683	102	76	46	.6	.7	.5	. 6
				Hg*	13.8	111	2.4	8.9	8.0	900	282	184	45	1.4	1.6	1.2	1.5
				Ma.†	18.1	121	3.8	10.9	9.0	1304	230	215	38	1.4	1.9	1.2	1.6
155	40	F	1.81	C	12.8	164	3.1	9.2	5.6	890	42	46	39	.3	.5	2	.3
				Ct.	26.6	137	14.0	11.4	8.3	3885	1340	1148	243	10.1	11.9	7.4	8.7
				C	10.4	148	1.7	8.2	5.5	492	19	13	42	.1	.1	.1	.1
				Hg	15.4	143	3.1	11.5	8.0	920	76	30	39	.5	. 3	.4	.2
lean v				0						1000		4.40		1.0	1.0		1.0
Chlor	rothiaz	ide		Control	16.4	124	4.2	11.4	9.2	1222	154	143	51	1.0	1.3	.8	1.2
				500 mg. i.v.	22.8	103	10.9	10.9	10.4	3225	1142	934	183	9.4	9.1	8.2	9.3
Mera	lluride			Control	16.0	126	4.8	11.2	8.6	1329	227	83	41	1.8	.6	1.5	.6
				2 ml. i.v.	23.8	142	7.4	16.5	12.3	2056	508	193	37	3.8	1.9	3.1	1.3

* C = average values obtained in control periods.

Ct. = average values obtained after administration of chlorothiazide 500 mg. intravenously.

Hg = average values obtained after administration of meralluride 2 ml. intravenously. Ma. = average values obtained after infusion of mannitol 4.7 per cent.

Ma. = average values obtained after infusion of mannitol 4.7 per cent.
 Data obtained during osmotic diuresis with mannitol are not included in the mean values.

‡ Patient with diabetes insipidus.

§ Patient on restricted sodium intake.

Mean value of only three patients.

thiazide. In contrast, administration of meralluride either did not induce any change in potassium excretion or caused some reduction.

Effect on Total Solute Clearance and Free Water Excretion. (Table 1, Figs. 1 and 2). The mean control osmolal clearance for all subjects was 4.5 ml./minute/1.73m² (range 1.7 ml./minute/1.73m² in a subject on restricted NaCl intake to 9.0 ml./minute/1.73m² in a subject excreting

considerable amounts of glucose during the experiment) with a simultaneous mean free water clearance of 11.3 ml./minute/1.73m² (range 3.7 to 19.1 ml./minute/1.73m²). Administration of chlorothiazide increased the mean solute clearance to 10.9 ml./minute/1.73m² (range 7.7 to 14.0 ml./minute/1.73m²); the mean free water clearance was 10.9 ml./minute/1.73m² (range 5.5 to 17.2 ml./minute/



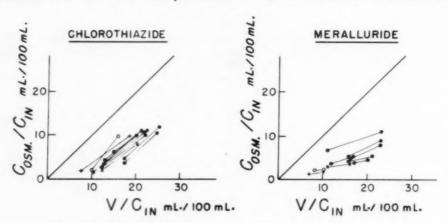


Fig. 1. Effect of administration of 500 mg, chlorothiazide or 2 ml, meralluride intravenously on urine flow and solute output. The total solute clearance (C_{OSM}) is plotted against urine flow (V). All values are expressed as per cent of the glomerular filtration rate. The first of the two points plotted in each instance represents the average of two or three control periods, while the second point is the average of two or three experimental periods. Chlorothiazide increased the urine volume to the same extent as meralluride but caused a greater increment in total solute excretion, and therefore did not produce an increase in free water clearance. The cross symbols and open circles represent the same patients studied with both agents.

1.73m²). Administration of meralluride increased the mean solute clearance to 7.4 ml./minute/1.73m² (range 2.4 to 14.3 ml./minute/1.73m²) and increased the mean free water clearance to 16.5 ml./minute/1.73m² (range 8.9 to 22.3 ml./minute/1.73m²).

In Figure 1 the change in osmolal clearance is plotted against urine flow. It can be seen that chlorothiazide and meralluride increase urine flow to a comparable degree. However, chlorothiazide caused a greater increment in total solute excretion and did not increase the free water clearance. In Figure 2 the increments in sodium and osmolal clearance after administration of chlorothiazide and meralluride are plotted against the increment in free water excretion. All values are expressed as per cent of the glomerular filtration rate. The figure clearly indicates that chlorothiazide increases sodium and total solute excretion more than meralluride, but at the same time produces a lesser rise in the percentage of free water excreted.

Data from a representative patient are given in detail in Figure 3, illustrating the effects of 500 mg. of chlorothiazide and 2 ml. of meralluride administered intravenously on separate days under similar experimental conditions. Both agents increased urine flow to a comparable extent. However, chlorothiazide increased total solute clearance, and the rate of sodium, potassium and chloride excretion to a greater degree than meralluride. Consequently, the fraction of free water excreted was decreased by chlorothiazide and was appreciably increased by meralluride. The difference between meralluride and chlorothiazide in their effect on free water excretion persisted during the subsequent infusion of isotonic mannitol, suggesting that the observed difference was independent of the solute load.

Chlorothiazide was administered to one subject with diabetes insipidus (patient 7) and failed to increase the excretion of free water. In contrast, patients with this syndrome given meralluride [7] respond with increased free water excretion.

Effects of the Combined Administration of Meralluride and Chlorothiazide. (Table II). In one subject chlorothiazide was given fifteen minutes after a typical response to meralluride had been induced. Although the administration of chlorothiazide led to a further marked increase in total solute excretion, the urine flow increased only slightly, and the absolute amount of free water excreted was considerably reduced. Under these circumstances chlorothiazide failed to exhibit its typical kaliuretic effect.

COMMENTS

The administration of chlorothiazide during water diuresis is characterized by (1) increased urine flow and solute output; (2) unchanged or diminished free water excretion; and (3) moderately reduced glomerular filtration. The administration of meralluride under similar conditions produces (1) a similar increase in urine flow, and a lesser rise in solute output; (2) increased free water excretion; and (3) no significant change in glomerular filtration.

The observed differences may provide information which allows one to differentiate the sites of action of the two compounds in the renal tubule. It is apparent that, irrespective of differences in effect on glomerular filtration, both mercurial diuretics and chlorothiazide act by inhibiting reabsorption of electrolyte in the renal tubules, but there is a distinct difference in their effects on free water clearance. As stated in the introdution, free water is considered to be produced by a distal tubular, selective electrolyte reabsorptive mechanism which, under circumstances of water diuresis, can reabsorb sodium and chloride without accompanying isosmotic amounts of water. Inhibition of this distal, solute-reabsorptive process should thus reduce the amount of free water excreted. In contrast, solute reabsorption in the proximal tubule is assumed to be isosmotic. Consequently, inhibition of proximal tubular reabsorption alone would either release isosmotic fluid for excretion (no change in free water excretion) or permit selective distal tubular reabsorption of solute, leading to increased free water excretion. Thus, during water diuresis, an increase in both the solute and free water clearance could be produced only by inhibition of isosmotic solute reabsorption in the proximal tubule, leading to diversion of more electrolyte and water to the distal tubule (selective) mechanism. In consequence, more electrolyte would be reabsorbed and more free water formed in the distal tubule (assuming no drug effect at this site). The assumption of solely proximal inhibition and diversion of electrolytes for more distal (selective) reab-

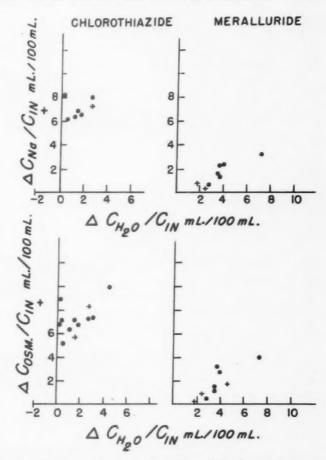


Fig. 2. The increments in sodium (ΔC_{Na}) and in total solute (ΔC_{O8M}) clearance following administration of either chlorothiazide or meralluride are plotted against the increment in "free water" excretion (ΔC_{H_2O}). All values are expressed as per cent of the glomerular filtration rate. It is apparent that chlorothiazide increases sodium and total solute excretion to a greater degree than meralluride. However, after administration of chlorothiazide there is a lesser increase in "free water" excretion than that observed after meralluride. The cross symbols represent individual studies with both agents.

sorption appears best to explain the findings with meralluride. During water diuresis, the effects of meralluride thus resemble those of an osmotic diuretic (mannitol), which also leads to in-

Table II

EFFECT OF COMBINED ADMINISTRATION OF MERALLURIDE AND CHLOROTHIAZIDE ON SOLUTE,

ELECTROLYTE AND WATER EXCRETION

Protocol	V (ml./ min.)	CIN* (ml./ min.)	Cosm* (ml./ min.)	CH ₂ O* (ml./ min.)	C _{H2O} /C _{IN} (%)	UOSMV (µOSM./ min.)	U _{Na} V (μEq./ min.)	U _{Cl} V (μEq./ min.)	U _K V (μEq./ min.)	C _{Na} * (ml./ min.)	Cci* (ml./ min.)	C _{Na} /C _{IN} (%)	C _{CI} /C _{IN} (%)
Control Meralluride (2 ml.). Chlorothiazide (500 mg.).	9.7	129	2.7	8.3	6.4	661	190	132	34	1.6	1.5	1.2	1.2
	18.0	133	6.8	14.4	10.8	1460	428	337	39	3.8	3.9	2.8	2.9
	19.5	109	9.8	11.8	10.8	2530	1040	667	49	9.1	7.8	8.4	7.1

^{*} Corrected to 1.73m² body surface area.



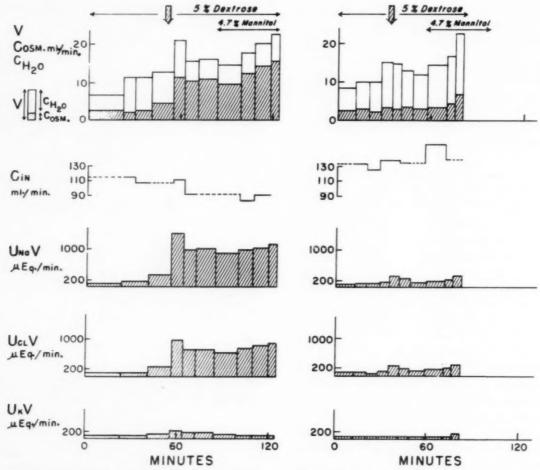


Fig. 3. Data from a representative patient are presented in detail. The effects of administration of chlorothiazide 500 mg. intravenously (left) are compared with the effects of meralluride 2 ml. (right) given under similar conditions on different days. Both agents increased urine flow to a comparable degree. However, chlorothiazide increased total solute clearance and the rate of sodium, potassium and chloride excretion to a greater degree than meralluride. Consequently, the fraction of "free water" excreted was not increased by the administration of chlorothiazide but was appreciably increased by the administration of meralluride. After the administration of mannitol the differences in effect on "free water" excretion of the two agents persisted, suggesting that the observed differences were independent of solute load.

creased free water formation, presumably by the same mechanism—the presentation of increased quantities of reabsorbable solute to the distal tubule [7].

The large increase in isosmotic solute excretion following administration of chlorothiazide is evidence for marked inhibition of electrolyte reabsorption in the proximal tubule. However, the solute diuresis induced by chlorothiazide is not associated with an increase in free water excretion. This observation seems best to be explained by assuming also an additional inhibition of the selective reabsorptive process in the distal tubule. (Fig. 4.) Chlorothiazide, in contrast to meralluride, thus appears to act on electrolyte reabsorption in two segments of the

renal tubule. This interpretation is supported further by the observed additive effects of chlorothiazide and meralluride. (Table 11.) If chlorothiazide is administered during a meralluride diuresis, the output of solute is markedly increased but the excretion of free water is actually reduced. These data suggest again that reabsorption in the proximal tubule is inhibited further by chlorothiazide and that selective reabsorption in the distal tubule also is blocked. In addition, recent observations made with another technique also support the concept that chlorothiazide, unlike meralluride, acts in both the proximal and distal portions of the nephron [15].

In one case (patient 15) after prolonged so-AMERICAN JOURNAL OF MEDICINE

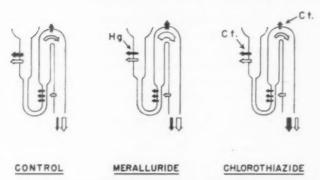


Fig. 4. Diagram showing the assumed action of chlorothiazide as compared to meralluride on the reabsorption of solutes (\rightarrow) and water (\Rightarrow) during water diuresis. During water diuresis dilute urine is produced by the selective reabsorption of solutes in the distal tubule. Meralluride partially inhibits proximal (isosmotic) sodium and/or chloride reabsorption, diverting more solutes to the distal tubule. Here the solutes are reabsorbed selectively, leading to free water formation. Chlorothiazide seems to inhibit electrolyte reabsorption both in the proximal and distal tubule, preventing an increase in excretion of free water, despite a marked rise in total solute clearance.

dium deprivation the characteristic inhibition of free water formation by chlorothiazide was less apparent. In this instance distal reabsorptive capacity may have increased as a result of sodium deprivation, thus allowing more free water formation to occur even in the presence of chlorothiazide. In this sodium-depleted patient chlorothiazide produced a much greater increase in excretion of solute (fivefold) and a lesser increase in excretion of free water than did meralluride.

Recently, evidence has been obtained [16,17] which suggests the presence in the loop of Henle of a third sodium (chloride) reabsorptive mechanism, the activity of which appears to be a prerequsite for the operation of a urine-concentrating mechanism located in the adjacent collecting ducts. Active and selective reabsorption of solute in the loop of Henle is assumed to result in an increased sodium content of the interstitial fluid of the papillae. This hypertonic interstitial fluid creates an osmotic gradient for water reabsorption as the urine passes through the adjacent collecting ducts. Theoretically, therefore, any agent which blocks electrolyte reabsorption in the loop of Henle might reduce maximal urine concentration. To test this hypothesis the effect of chlorothiazide on the capacity for water reabsorption (T_{H2O}) was investigated. (Fig. 5.) Chlorothiazide, like meralluride [14], did not reduce the T_{H₂O}, and it

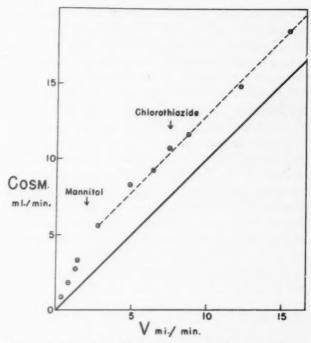


Fig. 5. Failure of administration of 500 mg. chlorothiazide intravenously to alter active water reabsorption ($T^{\rm e}_{\rm H_2O}$) during antidiuresis. Hypertonic mannitol (10 per cent) infusion was maintained from the time indicated. The $T^{\rm e}_{\rm H_2O}$ was not reduced by the administration of chlorothiazide in this subject.

may tentatively be concluded that the compound does not block sodium reabsorption in the loop of Henle. It is possible that protracted administration may produce changes which are insufficient in magnitude to be detected in a short-term experiment.

In the present study chlorothiazide appeared to exert its major effect on the excretion of sodium and chloride. Except for one instance the rate of sodium excretion always exceeded that of chloride. The large amount of chloride uniformly found in the urine precludes a predominant effect on bicarbonate reabsorption. From the available data one cannot definitely ascertain whether or not chlorothiazide acts primarily to inhibit sodium or chloride transport, but a primary effect on sodium ion transport is suggested by the fact that sodium is usually more abundant in the urine than chloride, and that inhibition of sodium reabsorption with diversion of sodium to a distal site could also account for the kaluria.

In these short-term experiments chlorothiazide almost uniformly produced a marked increase in urine potassium, whereas the potassium output was not increased, or actually decreased, after administration of meralluride.

However, the increased potassium excretion represented only a small fraction of the total increment in urine solute content and thus was not of sufficient magnitude to account for the reduced free water excretion observed after chlorothiazide. The kaliuresis following administration of chlorothiazide could be secondary to proximal inhibition of sodium reabsorption with consequent increase in the amount of sodium presented in the distal tubule for exchange with potassium. Potassium depletion following prolonged administration of chlorothiazide conceivably may also lead to a disturbance in the urine-concentrating mechanism [17]. Mercurial diuretics also can produce potassium depletion and hypokalemic alkalosis [18]. However, since the excretion of potassium presumably is entirely dependent on ion exchange with sodium, the induced potassium loss noted after protracted administration of mercurial diuretics might be secondary to the induced state of sodium depletion. Thus the similarity in longterm effects of the two diuretic agents does not necessarily invalidate the concept that the two compounds are qualitatively different in their mode of action.

It is necessary to consider also the hemodynamic effects of chlorothiazide. The compound led to a prompt, sustained decrease in glomerular filtration rate. This effect on glomerular filtration rate remains unexplained, but does not appear to be the result of either reduced arterial pressure or decreased extracellular fluid volume. Reduction in glomerular filtration rate during water diuresis has been shown to reduce the total solute output and urine flow [19]. However, chlorothiazide, despite its effect on glomerular filtration, increased solute output and urine flow. Therefore, the effects on free water excretion following administration of chlorothiazide are apparently not dependent on changes in the glomerular filtration rate, but result from changes in the tubular reabsorption of solutes and water.

The observations made in the present study may permit a more rational approach to the management of certain clinical situations. For example, free water formation may be reduced whenever there is decreased delivery of reabsorbable solute to the distal tubule. This can occur with a reduced glomerular filtration, as in congestive heart failure, or with increased proximal reabsorption of electrolyte, as in normal subjects during sodium deprivation, and in

the sodium-retaining states of nephrosis, cirrhosis and heart failure. It is conceivable that under these circumstances mercurial agents may be relatively ineffective because reabsorption of electrolytes is inhibited only in the proximal portion of the nephron. Avid distal tubular reabsorption occurring in these sodium-retaining states might then lessen the benefit of the mercurial agent.

The study also suggests that in some circumstances the combination of a mercurial agent and chlorothiazide may be more effective than either agent given alone. Proximal inhibition by the mercurial agent is added to the proximal and distal action of chlorothiazide. In addition, a more ideal diuresis may result because the excessive potassium loss of chlorothiazide appears to be prevented by prior administration of a mercurial agent. This has also been observed in animal experiments [15].

The potent kaliuretic action of chlorothiazide demonstrated in these experiments emphasizes again the potential hazard of potassium depletion with continued use of chlorothiazide. The study also suggests that in states of hypo-osmolality (hyponatremia) chlorothiazide should be used judiciously, since the compound promotes a relatively greater excretion of solute and a lesser excretion of free water than does meralluride.

SUMMARY

Chlorothiazide was given intravenously to a group of normal human subjects and to one patient with diabetes insipidus, and its effects on renal function were compared with those of meralluride administered under similar circumstances.

Following the administration of chlorothiazide, the urine flow and solute output increased but the free water clearance did not increase. Administration of meralluride was followed by a comparable increase in urine flow, a lesser rise in solute output, and an increased excretion of free water.

Chlorothiazide produced a considerably greater increase in solute (sodium chloride) excretion than did meralluride. This difference was particularly evident in a sodium-depleted subject. The natriuretic effects of chlorothiazide occurred despite an average reduction in the glomerular filtration rate of 16.9 per cent.

Chlorothiazide also promoted the excretion of potassium, whereas meralluride had little effect on potassium excretion.

When given together, the response to meralluride and chlorothiazide appeared to be additive in respect to total solute excretion. However, the potassium diuresis of chlorothiazide was prevented by previous administration of a mercurial agent.

The findings perhaps suggest the presence of more than one renal transport mechanism concerned with the reabsorption of strong monovalent electrolytes. The observations can be explained by the hypothesis that meralluride acts only in the proximal tubule, while chlorothiazide affects solute (sodium and chloride) reabsorption both in the proximal and in the distal segments of the nephron.

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Body Fluid Alterations During the Development of and Recovery from Hyponatremia in Heart Failure*

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THE association of hyponatremia, edema and sodium retention in certain disease states is an apparent paradox. Particular attention has been drawn to the presence of low serum sodium concentrations in certain patients with severe congestive heart failure [1,2]. Earlier reports ascribed this abnormality to sodium depletion induced by dietary restriction and the administration of mercurial diuretics, and advocated correction of the serum hypotonicity by the infusion of hypertonic sodium chloride solution [3-5]. It has since been clearly demonstrated that the body sodium stores are increased in the hyponatremic, edematous cardiac patient [6,7], and that treatment with hypertonic saline solution is generally unavailing and often harmful [1,2,8]. In contrast, correction of the hyponatremia and clinical improvement have been observed to result from successful mercurial diuresis [9], thus shifting the therapeutic emphasis from attention to the hyponatremia per se to the treatment of the underlying heart failure. While understanding of the clinical significance and the management of the hyponatremic cardiac patient has advanced, knowledge of the disturbances in body fluid and electrolyte metabolism associated with development of or recovery from this syndrome has remained scant.

The present report deals with studies in a group of patients with advanced cardiac disease and congestive failure. Detailed metabolic observations have been made during the development of hyponatremia and during the restoration of a normal serum sodium concentration. The results emphasize the complexity of this

problem and indicate that factors influencing both external balances of water and electrolytes and the internal distribution of cations are operative in this syndrome.

METHODS

All subjects were hospitalized in a metabolic ward, where measurements of water, sodium, potassium, chloride, and nitrogen balances were taken. The balance procedure and analytical methods have been outlined in previous reports from this laboratory [10,11]. All potassium balances reported have been corrected for nitrogen balance, utilizing the factor of 2.7 mEq. of potassium per gm. of nitrogen. Nitrogen balances were corrected for changes in the blood urea nitrogen concentration. Such corrections were small. A constant daily skin loss of 3 mEq. of sodium and chloride was assumed, and utilized in the calculation of the balances of these electrolytes.

Changes in extracellular fluid volume were derived from changes in the chloride space. Body water balances were calculated from weight changes after correction for fat and protein balance, by the method of Newburgh [12]. Chloride space changes were back calculated from an assumed value of 20 per cent of the body weight in the non-edematous state, and total body water was similarly back-calculated from an assumed value of 60 per cent of body weight. Cation transfers between the intracellular and extracellular fluid compartments were calculated by standard methods [13].

In order to assess the effect which external water and electrolyte balances exerted on changes in serum electrolyte concentrations, certain additional calculations have been made. The product of the estimated total body water and the extracellular fluid cation concentration (serum sodium concentration × 0.95/

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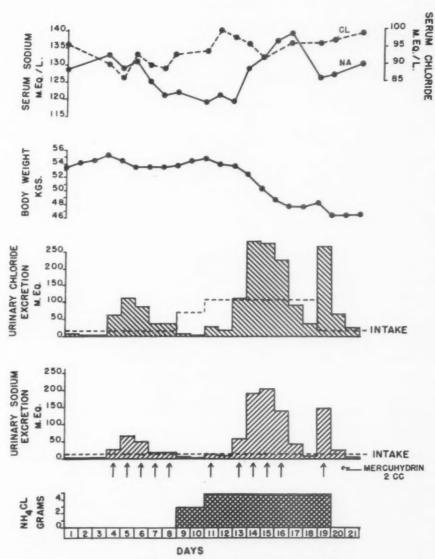


Fig. 1. Metabolic observations in subject A. R.

0.93 + 10 mEq. per L.) has been calculated, and will hereafter be designated as the "total body fluid cation." Total body fluid cation therefore represents total osmotically active cation calculated from only one concentration parameter, that of sodium in the serum. It is an arbitrary value, useful for purposes of comparison with the external balances of fixed cation (sodium and potassium) in evaluating the changes in serum electrolyte concentrations in this study. As will be discussed later, large discrepancies between external balances and changes in total body fluid cation have been interpreted as evidence for some intracellular alteration resulting in a change in osmotic pressure in the body fluids.

PROCEDURES AND RESULTS

Observations on the Development of Hyponatremia. Balance studies have been made in a patient June, 1959

(A. R.) with advanced coronary artery disease and congestive heart failure. These were initiated at a time when the patient manifested a mild hyponatremia. (Fig. 1.) On two occasions during the course of study there was an abrupt fall in the serum sodium concentration. The detailed data from these two periods (days 6 and 7, and days 17 and 18 of the study) are contained in Table I.

It should be noted that on days 6 and 7, when the serum sodium concentration decreased from 131 to 121 mEq. per L., the patient received intravenous injections of 2 ml. of Mercuhydrin® each day. The diuretic response was minimal, and no significant change in total body water, chloride space, cell water compartment or potassium balance occurred. A total

Down	Body		Total Ba	alances	Serum Electrolytes (mEq./L.)				
Days	Weight (kg.)	Na (mEq.)	Cl (mEq.)	K (mEq.)	N (gm.)	Na	Cl	К	CO
6 and 7	53.76 53.63	-53 	- 96	+3	+0.2	131 121	93 89	4.9	30 26
17 and 18	47.60 48.24	-35	+81	+52	+2.2	139 126	96 96	4.4 5.3	29 25

Derived Data

	Δ Body	ΔCl	Δ Cell	Δ Extracellula		Δ Calculat		Δ Calculated		Δ Total Body Fluid Cation
Days	Water (ml.)	Space (ml.)	Water (ml.)	Na (mEq.)	K (mEq.)	Na (mEq.)	K (mEq.)	Total Body Fluid Cation (mEq.)	Balances Na ⁺ K (mEq.)	Unaccounted for by External Balances (mEq.)
6 and 7 7 and 18	+130 +840	-60 +750	+190 +90	-207 -116	0 +19	+154 +81	+3 +33	-353 -287	-50 +17	-303 -304

negative balance of 53 mEq. of sodium was observed.

In contrast, no mercurial diuretic therapy was given on days 17 and 18, during which the serum sodium decreased from 139 to 126 mEq. per L. The patient was receiving 4.9 gm. of ammonium chloride per day at this time. As noted in Table I, a moderate increase in body water, accounted for by expansion of the chloride space, was observed. The net external balance of fixed cation (sodium and potassium) was negligible. This episode of hyponatremia immediately followed a successful mercurial diuresis, during which the serum sodium concentration had risen to a normal level (vide infra).

Calculation reveals that the retention of water on days 17 and 18 and the small external loss of sodium on days 6 and 7 account for only a small fraction of the observed changes in the serum sodium concentration. The development of hyponatremia is largely accounted for by some internal alteration in electrolyte metabolism. In each period a marked decrease, 303 and 304 mEq. respectively, in the calculated total body fluid cation occurred, which could not be attributed to the external electrolyte balances.

The Correction of Hyponatremia. Observations have been made during the correction of hyponatremia in four patients with congestive heart failure. A. R., who has been discussed in the previous section, had arteriosclerotic heart disease, and I. I., E. B. and E. D. suffered from advanced rheumatic valvular heart disease. Correction of hyponatremia accompanied the administration of mercurial diuretics in subjects A. R., I. I. and E. B., whereas E. D. received no diuretic therapy. The pertinent balance data and derived calculations on these subjects are given in Table II, and the data on subject A. R. are charted in Figure 1.

In no instance was sodium retention itself of primary importance in the correction of the hyponatremia. Only E. B. in period 1 showed a significantly positive external balance of sodium, and this factor alone, without concomitant potassium retention and water loss, would result in a negligible rise in serum sodium concentration. In every subject there was either a loss of body water associated with a positive cation balance (E. D., E. B. period 1) or a loss of fluid which was hypotonic with respect to the cation concentration in the serum. The disproportion

TABLE II

METABOLIC CHANGES DURING THE CORRECTION OF HYPONATREMIA

Balance Data

Subject	Days	Body Weight	Diuretic		Balances	per Period			Serum E (mEq	lectrolyte./L.)	es
Subject	Duys	(kg.)	Therapy	Na (mEq.)	Cl (mEq.)	K (mEq.)	N (gm.)	Na	Cl	K	CO2
A. R.	4	53.66 47.60	Hg ⁺ NH ₄ Cl	-559	-475 	-142	-1	119 139	98 96	4.6	22 29
I. I.	3	54.51 50.82	Hg	-134	-354	-66	-17 	128 139	90 92	5.4 3.4	32 35
Е. В.											
1	4	53.22 51.98	Hg	+69	-39	+50	-25	120 128	94 97	5.4	19 25
11	1	51.14 49.52	Hg ⁺ ACTH	-79	-239	-88	-6	127 136	100 100	5.2	25 30
E. D.	5	60.25 59.20	0	+4	-2	+109	_9 	128 138	100 103	3.4 5.0	18 27
					Derive	d Data					
				Δ Extrace	llular	Δ Cell	A Ca	lculated	External	Δ Tota	al Body

C I	Δ Body	ΔCI	Δ Cell	Δ Extra	cellular	Δ	Cell	Δ Calculated	External	Δ Total Body Fluid Cation
Sub- ject	Water (ml.)	Space (ml.)	Water (ml.)	Na (mEq.)	K (mEq.)	Na (mEq.)	K (mEq.)	Total Body Fluid Cation (mEq.)	Balances Na ⁺ K (mEq.)	Unaccounted for by External Balances (mEq.)
A. R.	-5610	-3680	-1930	-114	-20	-445	-122	-105	-701	+596
. I. E. B.	-3360	-3860	+500	-325	-54	+191	-12	-80	-200	+120
I	-740	-840	+100	+25	-7	+44	+57	+184	+119	+65
11	-1530	-2130	+600	-152	-28	+73	-60	+85	-167	+252
. D.	-510	-570	+60	+120	+29	-116	+80	+392	+113	+279

^{*} Intravenous Thiomerin® or Mercuhydrin.

between the balance of fixed cations and that of water resulted in an increased cation concentration in the body fluids, manifested in the serum by a rising sodium concentration.

A second factor influencing the serum sodium concentration appears from the discrepancy between the observed external sodium and potassium balances and the calculated changes in the total body fluid cation. In each subject (Table II) there is a rise in the cation concentration of the serum which cannot be entirely accounted for by external water and cation balances.

In Table III, that proportion of the rise in serum sodium concentration accounted for by

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external balances of water and fixed cation is shown for each experiment. These calculations were based on a calculated value for initial total body water. The remainder of the increase in serum sodium concentration is thought to be secondary to internal shifts of cation, occurring in response to osmotic alterations within the body cells. Considerable variation in the relative importance of these two factors in the correction of hyponatremia is apparent.

As shown in Table II, no uniform pattern of cellular water and electrolyte shifts is apparent during the correction of hyponatremia in this group of patients. The loss of cell water during diuresis in subject A. R. is unique; however a

TABLE III
PERCENTAGE OF INCREASE IN SERUM SODIUM
CONCENTRATION ACCOUNTED FOR BY (1) LOSS OF BODY
WATER IN EXCESS OF FIXED CATION AND (2) INTERNAL

CATION SHIFTS

Subject	Serum Na Increase	Account	ed for by:
Subject	(mEq./L.)	(1)	(2)
A. R.	20	6%	94%
I. I. E. B.	11	70%	30%
1	8	79%	21%
n	9	14%	86%
E. D.	10	43%	57%

gain in cell water of similar magnitude occurred during the preceding eight days. The calculated changes in cell water compartment in the remaining subjects are small and of questionable significance.

Striking clinical improvement accompanied the metabolic changes which have been presented. All subjects were previously considered in refractory heart failure, and showed massive edema, hepatomegaly, venous congestion and varying degrees of pulmonary congestion. In addition, I. I. and E. B. were lethargic and delirious at the onset of the study. The symptoms of congestive heart failure abated as the patients lost their edema, and they showed improved appetite, strength, and alertness. The delirium manifested by I. I. and E. B. cleared completely. The initial decline in serum sodium concentration to 119 mEq. per L. observed in A. R. was associated with increasing lethargy, which cleared after diuresis and correction of the hyponatremia. No mental symptoms were associated with the later decline (days 17 and 18) in serum sodium concentration. None of these patients manifested signs of peripheral vascular collapse, severe hypotension or marked oliguria. Moderate elevation of the blood urea nitrogen concentration was present in all, but in no patient did it exceed 50 mg. per 100 ml.

COMMENTS

The present data indicate that there are two factors operative during recovery from hyponatremia in congestive heart failure. The relative role played by each in any individual subject is variable. During correction of hypo-

natremia, each patient lost fluid which was hypotonic with respect to the fixed cation concentration in the extracellular fluid, or showed a positive cation balance associated with body water loss. As calculated in Table III, in three experiments (I. I., E. D., E. B. period I) the nature of the external cation and water balances accounted for a significant proportion of the observed rise in the serum sodium concentration. This was most evident in subject I. I. who lost body fluid with a fixed cation concentration of 60 mEq. per L. during a mercurial diuresis.

The nature of the measured external balances during recovery from heart failure suggests that these patients had previously retained water in excess of fixed cation. A defect in water metabolism associated with severe congestive heart failure has been amply demonstrated by other workers [14,15]. Although it has been suggested in metabolic studies [2], the development of hyponatremia in cardiac patients has not been conclusively and directly observed to result from primary water retention, with the exception of observations during the postoperative period following mitral commissurotomy [16]. Attempts in our laboratory to induce hyponatremia by oral water loading over a period of three to four days in two patients with advanced heart failure have been unsuccessful, since after an initial phase of water retention, water balance was again restored. Clinical observations indicate that the majority of patients with heart failure can tolerate rather large daily water loads without difficulty [17]. Nevertheless, the results of the present study and of those previously cited, indicate that water retention, despite sodium restriction, may occur in advancing heart failure and lead to dilution and hypo-osmolality of the body fluids. A review of the possible mechanisms concerned with the abnormal water metabolism in heart failure is not within the scope of this paper.

Of particular interest in the present study is the demonstration that changes in the body fluid composition occurred independent of external water and electrolyte balances. This was particularly notable in subject A. R., both during the development of and recovery from hyponatremia, as well as in E. D. and period II of E. B. In each instance, there was a large discrepancy between the calculated changes in total body fluid cation and the observed external cation balances. Unlike the external balances, the calculation of body fluid cation is indirect,

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utilizing an estimate of change in total body water which is subject to some error. An examination of the degree of the error involved, and its effect on the significance of the conclusions to be derived from these data seems warranted. Close agreement between body water changes calculated from caloric balance and those determined directly by deuterium oxide dilution has been previously demonstrated in this laboratory [11,18]. The error in the indirect estimation of fat balance has not exceeded 100 gm. per day. Errors of this magnitude would not appreciably affect the discrepancies between body cation changes and external balances in the short-term studies on A. R., E. D. and E. B. (Table 11.) Further substantiation of the significance of these results is provided by the fact that these discrepancies would be invalidated only if calculated water loss were grossly underestimated in these subjects. This would be possible only if the loss of body water exceeded the weight loss, such as would occur in subjects in positive caloric balance. Since each of these patients ingested a diet containing approximately 1,100 calories, it is certain that they were in negative caloric balance and that weight loss truly exceeded water loss to some degree. The significance of the discrepancies between calculated body cation changes and external balances in subject I. I. and period 1 of E. D. is less certain, but, as has been discussed, the external balances of water and electrolytes largely accounted for the observed rise in serum sodium concentration in these patients.

Assuming osmotic equilibrium between the extracellular and intracellular fluid compartments [19], the data suggest that some alteration in the osmotic activity of some portion of the body electrolytes has occurred in certain of these patients. Similar conclusions have been reached by other workers, in both clinical and experimental conditions [2,20-22]. Direct evidence concerning the site and nature of these osmotic alterations, and the stimuli which effect them are not attainable by the present method of study. Recent studies have cast considerable doubt on the possibility that the bone cortex acts as a sodium reservoir which serves to regulate the osmolality of the body fluids [23,24], making it most likely that these alterations occur within the body cells.

Some alteration of the intracellular solutes could result in diminished osmolality within the cells, and be manifested in the serum by hypo-

natremia. The nature of this alteration remains unknown, and could include changes in cation binding by intracellular proteins or other macromolecules, either resulting from a pH change or an alteration in the physical-chemical structure of these molecules, or be mediated by a change in valency or charge of the soluble intracellular anions. Linked as they are with energy metabolism within the cell [25], these anions might be affected by any serious disease state which interferes with the supply of energy substrate or the synthesis of cellular enzymes or other proteins concerned with energy metabolism. At present, our knowledge of the effects of severe or chronic disease on the cellular constituents and metabolic processes is too fragmentary to warrant direct application to the body fluid changes described herein.

The present study and that of Rubin and Braveman [9] clearly indicate that sodium retention is not necessary for the correction of hyponatremia in patients with cardiac edema. This suggests that prior sodium depletion, resulting from mercurial diuresis, is not the etiology of this syndrome. Studies of mercurial diuresis in patients with cardiac disease [10] and in a normal person, performed in our laboratory, have failed to reveal a loss of fixed cation in excess of body water in any instance, a pattern of excretion which must prevail if hyponatremia is to result directly from mercurial diuresis. An extrarenal toxic effect of the organic mercurials on certain body cells cannot be excluded, but the observation that correction of hyponatremia may occur during the administration of mercurial diuretics makes this possibility unlikely.

Care should be taken to differentiate the syndrome under discussion from that resulting from an apparent failure of renal sodium-conserving mechanisms in patients treated with diuretics. The latter patients manifest true dehydration and salt depletion, which serve to differentiate them from the type of patient included in the present study, in whom increasing cardiac decompensation and edema are the principal clinical features.

SUMMARY AND CONCLUSIONS

Metabolic studies have been conducted in a group of patients with advanced cardiac disease for the purpose of elucidating the abnormalities of fluid and electrolyte metabolism associated with the hyponatremia of heart failure. Data have been obtained from various studies, includ-

ing observations during the development of and recovery from hyponatremia. These indicate that abnormalities both in external excretion and internal distribution of water and electrolytes exist in these patients, either of which may be the predominant factor in the pathogenesis of this syndrome. A loss of water in excess of fixed cation has accounted for the correction of hyponatremia in certain subjects. It seems probable that primary water retention, leading to dilution of the body fluids, was at least partially responsible for the development of hyponatremia in these patients. In other subjects, discrepancies in serum electrolyte changes and external water and electrolyte balances indicate that an internal redistribution of electrolyte has occurred. These data are compatible with the view that metabolic alterations within the body cells, accompanying advanced disease, may be responsible for the hypotonicity of the body fluids observed in these patients. Further elucidation of the basic mechanisms involved in this phenomenon might be expected to yield information applicable both to normal human physiology and to the understanding of various abnormalities in body fluid composition associated with disease.

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Salicylate Intoxication with Special Reference to the Development of Hypokalemia*

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It is the purpose of this paper to discuss the manifestations of salicylate intoxication. The discussion will be based on six case reports, which will be used to illustrate the pathologic physiology of this disorder. Some of the major aberrations of acid-base balance produced by salicylate intoxication have been reviewed by Singer [1]. Hypokalemia as one of these aberrations has not been reported. The role of hypokalemia in the pathogenesis of some of the features of salicylate intoxication will be emphasized. Some of the therapeutic implications of the disorders of physiology will be discussed.

METHODS AND MATERIALS

The first four patients in this series were treated in the medical wards of the Peter Bent Brigham Hospital and were under our direct care. Patient 5 (P. W.) was cared for by physicians in another hospital but some of the biochemical studies were performed in our laboratory. Patient 6 (J. D.) was studied by Campbell and Maclaurin, and her case history has recently appeared in the *British Medical Journal* [2]. Her data are used with their kind permission.

The studies in the first five patients were performed during the acute phase of their illness. No planned protocol was used, but studies were performed as dictated by the clinical status of the patient. The determinations of blood gases, pH, sodium, potassium, and uric acid were performed in a research laboratory with research precision. The remainder of the determinations were performed in a routine hospital laboratory.

Arterial and urine pH's were measured anaerobically by means of a Beckman pH meter at room temperature and corrected to body temperature by the method of Rosenthal [3]. Total blood carbon dioxide was measured in a Van Slyke apparatus by the method

of Van Slyke and Neill [4]. Arterial CO₂ tension was calculated from these values by the Henderson-Hasselbalch equation. Blood and urine sodium and potassium were determined by the use of a flame photometer. Serum and urine uric acid determinations were performed using the uricase method of Praetorius and Poulsen [5].

CASE REPORTS

Case I. R. G., an eighteen year old white girl, ingested approximately 50 gm. of aspirin (150 tablets). Eight hours after ingestion, the patient was found comatose. She was admitted to another hospital where she was found to be unconscious. Her temperature was 106°F. She had Kussmaul's respiration at a rate of 44 per minute. A serum CO₂ combining power was found to be 8 mEq./L., and her urine was positive for reducing substance. Because of presumed metabolic acidosis, she was treated intravenously with small amounts of sodium bicarbonate. She continued to deteriorate clinically, and was transferred to the Peter Bent Brigham Hospital.

On admission, physical examination revealed the following: the temperature was 104.5°F.; pulse, 140; respiration, 44; and blood pressure, 104/50 mm. Hg.

The patient was flushed, hyperventilating, and responded only to painful stimuli. Aside from tachycardia and bounding pulses, examination of the heart and lungs was within normal limits. The deep tendon reflexes were absent. The pertinent laboratory findings on admission are shown in Table 1, which also summarizes the biochemical studies during the first three hospital days. An electrocardiogram (Fig. 1A) showed a sinus tachycardia, low voltage, QT prolongation, ST depression, and prominent U waves consistent with hypokalemia.

Initial therapy consisted of alcohol sponging for hyperpyrexia, and potassium chloride (40 mEq./L.)

^{*}From the Department of Medicine, Harvard Medical School and the Medical Clinics of the Peter Bent Brigham Hospital, Boston, Massachusetts. This investigation was supported in part by a research grant (H-2243) from the National Heart Institute of the National Institutes of Health, Public Health Service and in part by a grant from the Massachusetts Heart Association.

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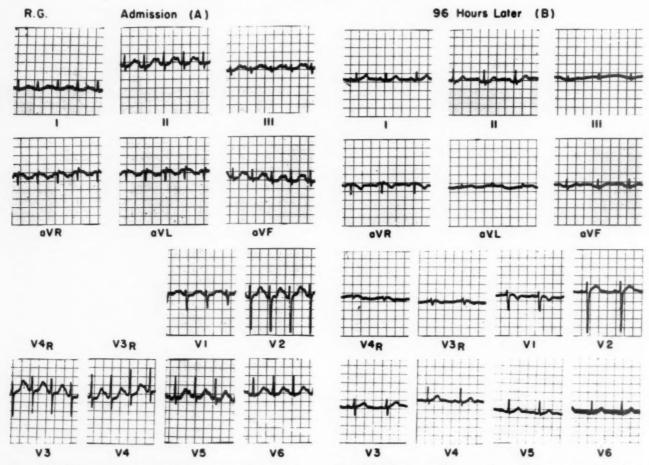


Fig. 1A. Electrocardiogram of patient R. G. taken on admission showing sinus tachycardia, low EMF, prolongation of QT, depression of ST and prominent U waves. Serum potassium 2.4 mEq./L.

Fig. 1B. Electrocardiogram ninety-six hours later showing normal curves. Serum potassium 3.6 mEq./L.

and 5 per cent glucose in water administered intravenously. The therapeutic response was dramatic. After the first 60 mEq. of potassium chloride, the pa-

tient's reflexes had returned and were normal. Arterial pH had fallen from 7.61 to 7.56 and her arterial CO₂ tension had risen from 10 to 19 mm. of Hg. She received a total of 360 mEq. of potassium chloride during the first thirty-six hospital hours with

Table 1

LABORATORY DATA ON PATIENT R. G. DURING FIRST SEVENTY-TWO HOURS OF HOSPITALIZATION

Data	Admission	1 hour	2 hours	4 hours	14 hours	22 hours	48 hours	72 hours
Arterial pH	7.61		7.55	7.56		7.46		
CO ₂ tension (mm. Hg)	10		19	19		25		
CO ₂ content (mEq./L.)	11.0			1		15.0		18.4
Plasma potassium (mEq./L.)	2.4	2.5			2.5	2.6	3.6	3.6
Plasma sodium (mEq./L.)	145	141			144			139
Plasma chloride (mEq./L.)	115	113			114			118
Blood urea nitrogen (mg.%)	30				40			
Prothrombin time (%)	9	18						
Serum calcium (mEq./L.)	4.1							
Serum phosphorus (mEq./L.).	1.2							
Serum uric acid (mg.%)	0.1			* * * *	* * * *			
Plasma salicylate (mg. %)	90				21			<5
Urine pH	5.5			5.1		4.6	4.1	4.1

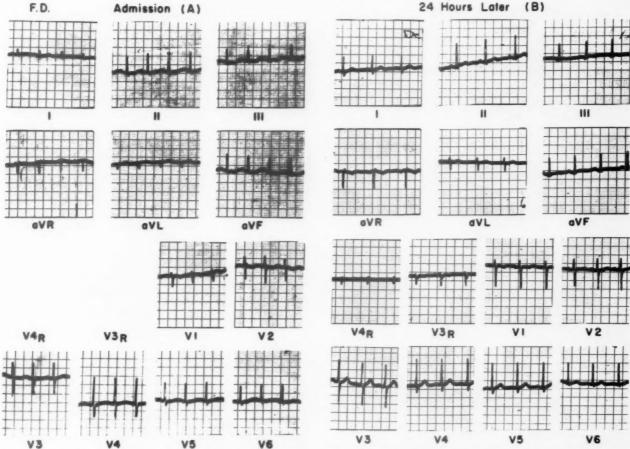


Fig. 2B. Electrocardiogram twenty-four hours later showing normal curves. Serum potassium was 3.5 mEq./L.

Fig. 2A. Electrocardiogram of patient F. D. taken on admission showing sinus tachycardia, long QT interval and depressed ST segments compatible with hypokalemia. Serum potassium 2.8 mEq./L.

no appreciable increase in serum potassium. Her serum potassium and electrocardiogram (Fig. 1B) did not return to normal until the fourth hospital day, although her arterial pH was essentially normal by the second day. By the fourth day, she had recovered clinically and her extracellular chemistry was normal.

CASE II. F. D., a nineteen year old white girl was transferred to the Peter Bent Brigham Hospital from another hospital. Twelve hours before admission to the outside hospital, she ingested approximately 33 gm. of aspirin (100 tablets). At the first hospital it was noted that she was markedly hyperpneic and drowsy. A blood salicylate level was 76 mg. per cent. Total plasma CO₂ content was 17 mEq./L. Her serum potassium was 3.1 mEq./L. and serum sodium was 148 mEq./L. Because it seemed that hemodialysis might be required, she was transferred to the Peter Bent Brigham Hospital.

Physical examination on admission revealed a young, semistuporous white girl with characteristic Kussmaul breathing. The deep tendon reflexes were absent. The remainder of the physical examination

was within normal limits. Laboratory studies revealed the following: arterial pH, 7.46; serum potassium, 2.8 mEq./L.; serum sodium, 142 mEq./L.; serum chloride, 119 mEq./L.; CO₂ combining power, 12.7 mEq./L.; blood urea nitrogen, 18 mg. per cent; prothrombin time, 21 per cent; urine pH, 7.0; and electrocardiogram (Fig. 2A), sinus tachycardia, prolonged QT interval, low T, and depressed ST segments consistent with hypokalemia.

The patient was treated intravenously with potassium chloride (120 mEq.), vitamin K (50 mg.) and 5 per cent glucose in water. In twenty-four hours the hyperpnea subsided, reflexes returned to normal, the electrocardiogram became normal (Fig. 2B), and the pertinent blood chemistries were as follows: arterial pH, 7.44; serum potassium, 3.5 mEq./L.; serum sodium, 140 mEq./L.; serum chloride, 106 mEq./L.; CO₂ combining power, 17.6 mEq./L.; and salicylate level, 0 mg. per cent.

Her recovery seemed assured without dialysis, and , she was transferred back to the referring hospital.

CASE III. B. W., a thirty year old white housewife, swallowed approximately 100 aspirin tablets about four hours before admission. She was found at home in

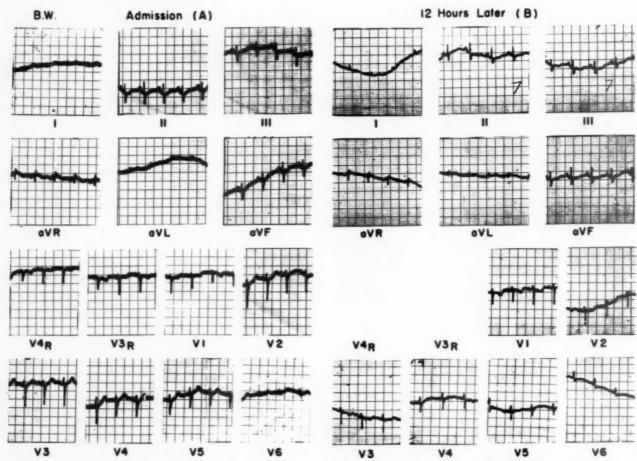


Fig. 3A. Admission electrocardiogram of patient B. W. taken four hours after ingestion of salicylate. No evidence of hypokalemia. Serum potassium 4.6 mEq./L.

Fig. 3B. Electrocardiogram twelve hours later showing emergence of U waves and flattening of T waves, suggestive of hypokalemia. Serum potassium 3.3 mEq./L.

a semicomatose state and brought to the hospital. In the emergency ward, 170 cc. of coffee ground, 2-plus benzidine positive material was aspirated by a stomach tube, and she was admitted.

Physical examination on admission revealed the

following: temperature 101°F., pulse 132, respiration 30, and blood pressure 120/60 mm. Hg. The patient was a thin, confused, thirty year old woman who was alternately drowsy and resistive. Respirations were Kussmaul in character. Neurological examination was

TABLE II
LABORATORY DATA ON PATIENT B. W. DURING THE FIRST SIXTY HOURS OF HOSPITALIZATION

Data	Admission*	8 hours	12 hours	16 hours	18 hours	20 hours	24 hours	60 hour
	*							
Arterial pH	7.60	7.60	7.60			7.61		7.51
CO ₂ tension (mm. Hg)	18		****	****				34
CO ₂ content (mEq./L.)	16.2							23.4
Plasma K (mEq./L.)	4.6	4.4	3.3	3.5	4.3	4.3	3.7	5.8
Plasma Na (mEq./L.)	144	140	131	141	135	135	136	138
Plasma Cl (mEq./L.)	110	103	100	106	104	105	107	102
Blood urea nitrogen (mg. %)	13			****	****		****	10
Prothrombin time (%)	80.0					12.5		88.0
Plasma salicylate (mg. %)	88		32			20		
Urine pH	7.30		4.50	5.00	6.20	7.00	5.00	5.00

^{*} Four hours after salicylate ingestion.

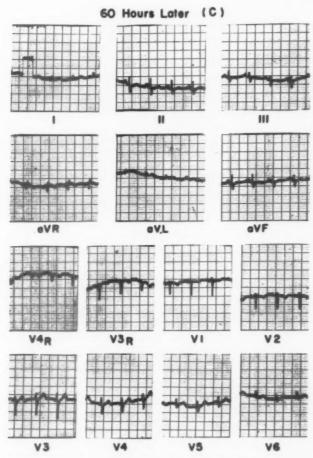


Fig. 3C. Electrocardiogram of patient B. W. sixty hours after admission showing recession of ST and U wave changes. Serum potassium 5.8 mEq./L.

within normal limits except for some obtundation. The reflexes were normal. Her laboratory studies on admission and during the first three days of hospitalization are summarized in Table II. An electrocardiogram (Fig. 3A) showed a sinus tachycardia with a short PR interval. There was no evidence of hypokalemia.

At first, oral administration of fluid and electrolyte replacement was attempted. During the first twelve hours, despite the oral administration of 60 mEq. of potassium, serum potassium remained essentially unchanged (4.6 to 4.4 mEq./L.) The arterial pH remained at 7.60, and the patient had electrocardiographic evidence compatible with hypokalemia. (Fig. 3B.) Potassium, 344 mEq., was administered during the next twenty-four hours, but her serum potassium fell from 4.4 to 3.5 mEq./L. Twenty-four hours after admission her prothrombin time fell from 80 to 12 per cent. Fifty mg. of vitamin K was administered intravenously, and twenty-four hours later her prothrombin time rose to 88 per cent. Urine pH fell from 7.3 to 4.5, despite the presence of respiratory alkalosis. By the third day, the patient had almost completely recovered. Arterial pH had fallen to 7.51, and her arterial CO₂ tension had risen to 35 mm. Hg.

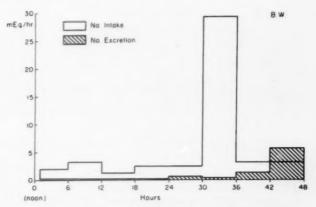


Fig. 4. Sodium balance of patient B. W.

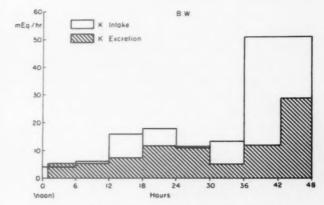


Fig. 5. Potassium balance of patient B. W.

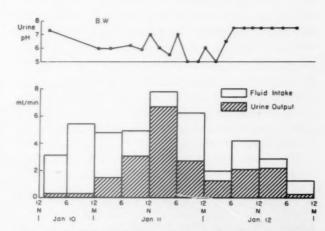
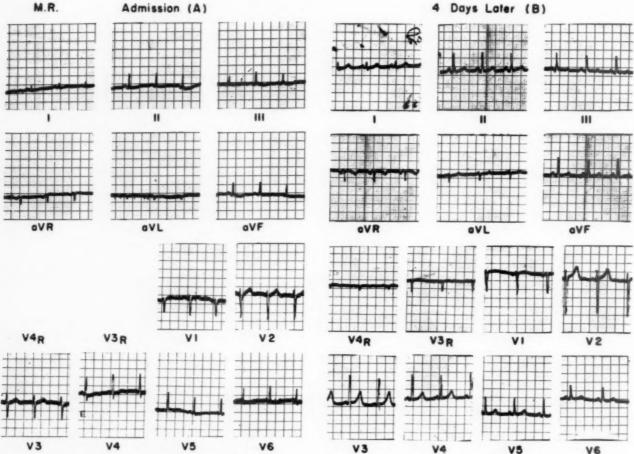


Fig. 6. Water balance and urinary pH of patient B. W.

Hyperventilation was no longer present and her temperature was normal. The electrocardiogram reverted to a normal tracing. (Fig. 3C.) Sodium, potassium, water balance and urinary pH studies made during the acute phase of the illness are shown in Figures 4, 5 and 6.

Case IV. Pneumonitis developed in M. R., a thirty-nine year old white housewife, one week before admission. She had been treating herself with aspirin



R. Fig. 7B. Electrocardiogram four days later showing normal curves. Serum potassium 5.1 mEq./L.

Fig. 7A. Admission electrocardiogram of patient M. R. showing low EMF, flat T waves, U waves, and slight ST depression compatible with hypokalemia. Serum potassium 3.1 mEq./L.

for symptomatic relief. Shortly before admission, her family noted that she was disoriented. It was also noted that ninety-six aspirin tablets were missing from a bottle near the patient's bed, and she was presumed to have taken them.

Physical examination revealed the following: pulse, 108; blood pressure, 90/60 mm. Hg; respiration, 40; and temperature, 100.5°F.

The patient was hyperpneic, disoriented and hyperkinetic. The lungs showed dullness and bronchial breathing at the right base. The reflexes were normal. Laboratory studies showed the following: arterial pH, 7.47; CO₂ tension, 30 mm. Hg; serum potassium, 3.1 mEq./L.; serum sodium, 151 mEq./L.; serum chloride, 116 mEq./L.; CO₂ content, 13 mEq./L.; prothrombin time, 16 per cent; blood salicylate level, 40 mg. per cent; urine pH, 4.5; fasting blood sugar, 78 mg. per cent; basal metabolic rate, plus 35 per cent; protein-bound iodine, 5.28 μg. per cent; and twenty-four-hour I¹³¹ uptake 24 per cent.

An electrocardiogram (Fig. 7A) was consistent with hypokalemia.

The patient was treated with 120 mEq. of potassium

chloride and 2 L. of 5 per cent glucose in water over the next twenty-four hours. On this therapy her potassium rose to 3.9 mEq./L., sodium dropped to 143 mEq./L., arterial pH fell to 7.42, and arterial CO₂ tension rose to 35 mm. Hg. Her electrocardiogram (Fig. 7B) reverted to a normal pattern. The patient was given 100 mg. of vitamin K intravenously which raised her prothrombin time from 16 to 50 per cent.

F Case v. P. W., a five year old girl, was being treated at an outside hospital for rheumatoid arthritis. She had been maintained on 10 mg. of prednisone per day. On this medication her rheumatoid arthritis became worse, and she was treated with 3 gm. of aspirin per day. After several days of therapy, marked hyperpnea, nausea, vomiting and drowsiness were noted. At this time the findings were as follows: arterial pH, 7.55; arterial CO₂ tension, 23 mm. Hg; serum potassium, 3.6 mEq./L.; serum sodium, 135 mEq./L.; serum chloride, 111 mEq./L.; total CO₂, 17 mEq./L.; blood salicylate level, 50 mg. per cent; and urine pH, 5.5.

She was treated with 750 cc. of 5 per cent glucose in water and 50 mg. of hydrocortisone intravenously. She continued to be hyperpneic and twelve hours

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Table III
LABORATORY DATA ON PATIENT J. D. DURING THE FIRST WEEK OF HOSPITALIZATION

Data	Admission	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Arterial pH	7.46	***	7.44				
CO ₂ tension (mm. Hg)	17		18				
Plasma K (mEq./L.)		3.6	3.0	2.9	5.8	5.0	4.2
Plasma Na (mEq./L.)		142	140	150	152	150	145
Plasma Cl (mEq./L.)		110	122	110	112	108	112
Blood urea nitrogen (mg.%)		325	255	183	100	66	39
Plasma salicylate (mg.%)				< 5			***

later developed generalized convulsions. At this time her salicylate level was noted to be 10 mg. per cent. Repeat blood studies were as follows: venous pH, 7.16; arterial CO₂ tension, 34 mm. Hg; serum potassium, 5.4 mEq./L.; serum sodium, 123 mEq./L.; serum chloride, 98 mEq./L.; and CO₂ content, 12 mEq./L.

In addition, a roentgenogram of the chest showed pulmonary congestion and edema. She was treated with 6 gm. of sodium bicarbonate, digitalization and penicillin. She responded rapidly to this therapy and made an uneventful recovery.

Case vi. J. D., a fifty-two year old unmarried woman, swallowed approximately 25 gm. of aspirin. Drowsiness and oliguria developed. On admission to the Middlesex Hospital, she was drowsy, confused and hyperpneic. During the first six hours in the hospital, she passed 740 ml. of urine which was acid in pH and contained protein, and hyaline and granular casts. Her clinical course was characterized by azotemia and weakness. She was treated with fluids and sodium and potassium replacement. On this regimen she improved progressively and was normal by the seventh hospital day. The laboratory data are summarized in Table III. It may be noted that serum potassium was low at a time when her arterial pH was essentially normal.

COMMENTS

The pathologic physiology of salicylate intoxication may be described under the following headings: (1) the stage of respiratory alkalosis, (2) the stage of metabolic acidosis, and (3) other manifestations.

The Stage of Respiratory Alkalosis. The earliest change in acid-base balance produced by the ingestion of large amounts of salicylate is the development of respiratory alkalosis [1]. The respiratory alkalosis results from the stimulation of the medullary respiratory center by this drug. Most observers agree that at least a partial explanation for this stimulation is that salicylates increase the sensitivity of the respiratory center

to CO₂/pH [6,7]. Whether or not this effect, like that of 2–4 dinitrophenol on respiratory center activity, may possibly be mediated by the effect of salicylate in stimulating metabolic oxidative reactions is conjectural [8].

The ability of salicylate to produce hyperventilation appears to be mediated by the anterior hypothalamus, since lesions in this area may reduce or totally abolish the stimulatory effect of salicylate on ventilation [9]. This hypothalamic area corresponds closely to that previously described by Guerra and Brobeck as responsible for the antipyretic effect of salicylates [10].

All six of the patients reported here showed respiratory alkalosis when first seen, with the initial arterial blood pH ranging from 7.46 to 7.60. Respiratory alkalosis is important first of all because it may be easily mistaken for metabolic acidosis. The resemblance between these two states is outlined in Table IV. It can be seen that the clinical features of these two states are remarkably similar. It can also be seen that urinary pH, which is frequently used to differentiate these two states, is an inaccurate guide to the pH of extracellular fluid during the respiratory alkalosis. This table emphasizes that the only reliable distinction rests on the value of arterial pH. This finding agrees with the study of Spector and McKhann [11]. They found acid reactions in most of the urine specimens of their cases of salicylate intoxication, although the blood pH was always over 7.45.

An important consequence of alkalosis is the development of hypokalemia. While the occurrence of hypokalemia in metabolic alkalosis is well characterized, little data is available on this phenomenon in respiratory alkalosis. McCance [12] demonstrated an increase in potassium excretion during respiratory alkalosis in normal

TABLE IV
THE DIFFERENTIAL DIAGNOSIS OF RESPIRATORY ALKALOSIS AND METABOLIC ACIDOSIS

Parameter	Respiratory Alkalosis	Metabolic Acidosis
Hyperventilation	Present, frequently of Kussmaul type (primary effect of precipitating agent)	Present, frequently of Kussmaul type (effect of H ⁺ in stimulating respira- tory center)
Appearance	Flushed, vasodilated	Flushed, vasodilated
Cardiovascular status	Bounding pulses, large pulse pressure, active apical impulse (high cardiac output with salicylate intoxication)	Bounding pulses, large pulse pressure active apical impulse (high cardiac output)
Total plasma CO ₂	Low (renal loss of bicarbonate)	Low (decreased bicarbonate with acidosis)
CO ₂ combining power	Low (renal loss of bicarbonate)	Low (decreased bicarbonate with acidosis)
Arterial CO ₂ tension	Low (hyperventilation)	Low (hyperventilation with acidosis)
Urine pH		Acid
Reducing substances in urine		Present if acidosis produced by diabetes mellitus
Arterial pH	High	Low

subjects, but not in subjects depleted of sodium. The studies of Elkinton et al. [13] on the acute metabolic effects of respiratory alkalosis showed little cellular and renal potassium shifts during voluntary hyperventilation. The mild intensity of the stimulus and the brief duration of the hyperventilation and the alkalosis in their studies probably readily account for the inability to demonstrate significant effects on potassium balance. In salicylate intoxication a very high respiratory minute volume (19 L./minute in patient B. W.) can be maintained for many hours, providing an intense alkalotic stimulus. The features of hypokalemia as seen in patients with the respiratory alkalosis of salicylate intoxication are the same as those of metabolic alkalosis, and the mechanism of production of potassium depletion is probably identical in the two forms of alkalosis.

The importance of hypokalemia in the respiratory alkalosis of salicylate intoxication is emphasized by its occurrence in all six patients reported here. This finding is consistent with the findings of Rapoport and Guest [14]. They showed that twenty-four hours after the administration of large doses of salicylates to dogs and monkeys potassium levels were regularly decreased, but commented no further on the significance of hypokalemia.

There are at least two factors responsible for the development of hypokalemia during alkalosis.* An alkaline pH tends to shift potassium out of the extracellular compartment [15]. This shift may produce hypokalemia without body potassium depletion. Hypokalemia may produce electrocardiographic and neuromuscular changes independent of changes in total body potassium stores. The second factor is that alkalosis may produce hypokalemia, and ultimately potassium depletion, because of excessive renal loss.

In the clinical manifestations of alkalosis, extrarenal factors are for the most part secondary to the renal response. The primary extrarenal factors are small. Studies in dogs with acute respiratory alkalosis in which nephrectomy was performed [16] demonstrated a small net increase of sodium and net loss of potassium in the extracellular fluid. In alkalosis occurring in the intact animal, however, the large renal stimulus for potassium secretion undoubtedly overwhelms these small extrarenal factors. During cellular dehydration and extracellular hyperosmolality, due to high sodium concentration, there is an increase in potassium excretion [17]. However the failure of this effect to occur when the hyperosmolality is due to mannitol or other solutes [18] suggests it is mediated through the kidneys secondary to the high rate of sodium reabsorption in the distal tubules. In the patients

^{*} Studies performed since this paper was written indicate that salicylates also have a direct effect on the renal tubular mechanisms involved in potassium excretion [40].

reported previously, gross dehydration was evident in all and a modestly increased serum sodium concentration was present in three patients (R. G., F. D., M. R.). This effect may have provided a small further stimulus to sodium reabsorption and potassium excretion in the distal renal tubule. The primary renal mechanism for the development of potassium depletion in alkalosis is related to the ion-exchange mechanism for the distal tubular reabsorption of sodium whereby potassium is secreted [19] into the urine and is closely involved in the mechanism for the acidification of the urine [20]. In the competition of potassium and hydrogen ions for sodium ion during the distal reabsorption of the latter in alkalosis, the deficit of hydrogen ion favors the exchange of potassium for sodium, leading to significant depletion of potassium ion from both the intracellular and extracellular spaces as a consequence of the alkalosis alone.

A further significant factor, undoubtedly operative in patients with salicylate intoxication, is the mutual aggravation of alkalosis and potassium depletion. With a stimulus for the renal secretion of potassium, the entrance of hydrogen ion into the intracellular compartment will aggravate the extracellular alkalosis, providing further stimulus for potassium depletion.

Hypokalemia appeared to play an important role in the clinical manifestations of salicylate intoxication. All six patients showed low serum potassium concentrations at some stage of intoxication. In the four patients in whom electrocardiograms were available, there were changes consistent with hypokalemia. With potassium administration, the electrocardiograms became normal. Patients R. G. and B. W. showed areflexia, which is known to result from hypokalemia. The areflexia responded dramatically to the administration of potassium.

Since isotope measurements of total body potassium were not performed in these patients, the evidence for potassium depletion is indirect. The presence of an acid urine pH in the face of severe extracellular alkalosis may be related to potassium depletion. It is well known that in other forms of alkalosis a "paradoxical" aciduria may occur [21]. Whether it is due to the potassium depletion primarily and the consequent decrease in relative availability of potassium ion in competition for hydrogen ion in the distal reabsorption of sodium [19], or due to the relative cellular acidosis consequent to the exchange between the extracellular and intracellular spaces of hydro-

gen ion for potassium ion during the development of potassium depletion and alkalosis [22] is not clear. The ultimate result, in either case, would be the production of an acid urine despite severe systemic alkalosis. This sequence of events is suggested by the course of patient B. W. She was seen at an earlier phase of her disease than any of the other patients in the series, entering the hospital four hours after the ingestion of salicylates. Her original urinary pH was alkaline (7.3) at a time when her serum potassium was normal (4.6 mEq./L.). When she was treated with inadequate amounts of potassium, her urine pH fell from 7.3 to 5.0, despite an arterial pH of 7.6. Her serum potassium was 3.3 mEq./L. at this time. With adequate potassium replacement, the serum potassium rose to 4.3 mEq./L. Her urine pH rose to 7.0. Potassium depletion is also indicated by the fact that in patients R. G. and J. D. hypokalemia and abnormal electrocardiograms persisted when arterial alkalosis was no longer present.

Relman and Schwartz [23] have observed renal tubular lesions in human subjects depleted of potassium. The studies of Welt and others have localized, in rats depleted of potassium, a lesion in the renal-collecting ducts well correlated with the loss of ability to concentrate the urine consequent to potassium depletion [24]. The fine mechanism of the polyuria and inability to concentrate the urine in potassium depletion in man is not completely clarified. In potassium depleted rats a lesion has been shown to involve the collecting duct system [24]. These observations correlate well with recent studies implicating this part of the nephron in the renal concentrating mechanism [25]. It is unclear how quickly potassium depletion leads to a deficient normal concentrating mechanism in humans. From the balance data on patient B. W., it is apparent that as potassium depletion developed, the rate of urine flow rose markedly and the urine osmolality fell to low levels despite incomplete correction of her general dehydration as judged clinically. Although the serum osmolality was not measured at the time of highest urine flow and lowest urinary osmolality, the administration of large quantities of potassium ion was quickly followed by a fall in urine volume and a rise in osmolality despite the approximately constant rate of water and solute administration.

An important therapeutic feature of the hypokalemia is illustrated by the balance data on patient B. W. These data show that during alkalosis a very large part of potassium, administered exogenously, will be excreted in the urine. Thus, in patients R. G. and B. W., approximately 350 mEq. of potassium/twenty-four hour period was required to restore a normal serum potassium level and to return the electrocardiogram to normal.

It seems clear that the stage of respiratory alkalosis during salicylate intoxication is accompanied by hypokalemia. The hypokalemia may be demonstrated by a low serum potassium, by electrocardiographic abnormalities, and by changes in neuromuscular function. Potassium depletion is presumably present as well and may explain the fact that urinary pH is usually acid, despite severe extracellular alkalosis. Large quantities of potassium are required to repair the depletion, both because of the magnitude of the loss and because of the enhanced urinary excretion of this ion.

A consequence of severe respiratory alkalosis may be the development of tetany. Tetany was not found in any of our patients, and to our knowledge has only been reported in one patient with salicylate intoxication [26]. The total serum calcium level was normal in the one observation made.

Another theoretical consequence of severe respiratory alkalosis may be interference with tissue oxygen transport. Alkalosis shifts the oxyhemoglobin dissociation curve to the left. For a given oxygen saturation, there is less oxygen available for diffusion into tissues. This factor would be of greater importance in salicylate intoxication than in other forms of alkalosis. As will be discussed later, salicylates act to stimulate cellular metabolism directly. In the face of increased oxygen demand and decreased oxygen supply, cellular hypoxia would appear to be an important consideration in this disorder. Although there are no data to document the clinical importance of this concept, oxygen by nasal catheter has been routinely administered to the more severely intoxicated subjects. In this way, the amount of oxygen in physical solution is increased and adequate tissue oxygenation made more likely.

Various therapeutic measures have been advocated in the stage of respiratory alkalosis. The administration of sodium bicarbonate or lactate has been advocated to hasten the excretion of salicylate and thereby terminate the hyperpnea [27]. These observations have been extended by other investigators and the beneficial effect of an alkaline urine (pH 7.5) may be

attributed to an increased secretion and decreased reabsorption of free salicylate [28,29]. However, these controlled studies have been conducted with only moderate salicylate loads producing serum levels of only 10 to 35 mg. per cent and the subjects have not had a decompensated respiratory alkalosis. During severe intoxication this form of therapy will accentuate the alkalosis already present and thus accentuate the physiologic defects. The development of tetany during bicarbonate administration in salicylate intoxication with death during convulsions has been reported in dogs [14]. Campbell and Maclaurin [2] and Harvie and Singer [30] raise substantial doubt as to the efficacy of this therapy. Its use does not appear to be well founded.

Inhalation of CO₂ rich mixtures (5 to 10 per cent CO₂ in air) has been recommended to restore extracellular pH to a normal level. The use of such therapy results in an accentuation of the hyperventilation already present. This form of therapy is poorly tolerated and is not recommended.

Respiratory center depressants can decrease the hyperpnea of salicylate intoxication. Salicylates, however, produce a direct stimulation of metabolic activity, and the hyperpnea may be regarded as a compensatory mechanism. A depression of ventilation, unless quantitatively geared to the increase in metabolism, may produce cellular hypoxia and/or respiratory acidosis. Rapoport and Guest [14] demonstrated enhanced toxicity of salicylates in dogs and monkeys when treated with respiratory center depressants. Therefore, in practice, central nervous system depressants are dangerous and the combination of salicylate intoxication and respiratory center depression may lead to irreversible cellular changes and death.

It is our impression that in the usual patient with salicylate intoxication, adequate fluid and potassium replacement is sufficiently supportive to allow the patient to excrete salicylates, thereby correcting his metabolic defects. On theoretical grounds, oxygen has been administered to the more severely intoxicated patients. In the patient in whom persistent azotemia and oliguria are related to renal damage, rapid removal of salicylates by hemodialysis can be accomplished. This form of therapy ideally should be performed during the first few days while a significant portion of the salicylate exists in the free unconjugated form [29,31]. This form of therapy has not been necessary in the patients reported here.

The Stage of Metabolic Acidosis. The metabolic

and clinical features of this stage of salicylate intoxication have been reviewed by Singer. In young children the stage of respiratory alkalosis is usually quite brief, and the patient frequently presents either in frank metabolic acidosis or with a mixture of respiratory alkalosis and metabolic acidosis. Of great interest is that patients recovering from the stage of metabolic acidosis frequently pass through a stage of respiratory alkalosis [1].

The mechanism of the metabolic acidosis is not known. It seems clear that it cannot be due to the salicylate ion itself [32]. It is usually not accounted for by ketosis, although some degree of ketosis may be present and the importance of ketosis during the stage of metabolic acidosis in young children has been emphasized by Winters [33]. It does not appear to be produced by renal failure, since renal failure occurs only rarely and is a very late complication of severe intoxication [1]. Among the suggestions that have been made are that it results from involvement of liver function [34]. Another suggestion has been made that, in reality, it is a respiratory and not a metabolic acidosis, occurring as a result of increased CO2 production in the face of an insufficiently augmented ventilation [7].

Although the mechanism of metabolic acidosis is unknown, several points concerning its management are pertinent. In the first place, the great rapidity with which respiratory alkalosis may change to metabolic acidosis should be emphasized. For example, in patient 5 the arterial pH changed from 7.55 to 7.16 in less than twelve hours. This change occurred without any obvious change in physical examination, or urinary pH. The rapidity with which the status of these patients may change emphasizes the importance of frequent observations of arterial pH as a guide to therapy. The second point to be emphasized is that effective therapy for this stage of the disorder is the use of adequate amounts of intravenous bicarbonate or lactate. Metabolic acidosis did not develop in any patient in the present series who received adequate potassium therapy. This circumstance may be entirely fortuitous.

Other Manifestations. A number of other manifestations of salicylate intoxication seem worthy of emphasis. One such manifestation is fever. Salicylate is ordinarily considered an antipyretic substance. Four of the six patients in this series had rectal temperatures greater than 100°F., and one patient (R. G.) had a temperature of 106°F. The presence of fever may be related to the

metabolic stimulation produced by salicylates or to a direct central effect of the drug.

Hypoprothrombinemia is a common finding in salicylate intoxication. Three of the four patients in whom measurements were made showed prothrombin times of less than 50 per cent. In no patient was there clinical evidence of bleeding as a result of the hypoprothrombinemia. Parenteral administration of vitamin K led to a rapid return of prothrombin times to normal values.

Hemorrhagic gastritis resulting in upper gastrointestinal hemorrhage has been emphasized as a manifestation of salicylate toxicity [35]. One patient (B. W.) showed a 2-plus benzidine reaction in the gastric aspirate. However, clinically significant upper gastrointestinal hemorrhage did not occur in the present series. It has also not been reported as a major complication of acute massive salicylate intoxication. Routine ulcer therapy as prophylaxis against bleeding is, however, probably advisable.

The elevated metabolic rate produced by salicylates and its implications for therapy have already been discussed. The similarity of this effect to the action of dinitrophenol has been emphasized previously by Sproull [36]. The elevation of metabolic rate appears to be a direct cellular effect of salicylate. It is independent of thyroid activity. The radioactive I¹⁸¹ uptake and protein-bound iodine were normal in the one patient studied.

Renal function is usually not markedly affected by salicylate intoxication, except for inhibition of the tubular reabsorption of urate. The magnitude of this effect and its relationship to salicylate levels is shown in Table v, which summarizes data obtained in patient R. G.

The initial serum uric acid level of 0.1 mg. per cent is strikingly low, being the lowest value that has been found in a search of the available literature. The elevation of the ratio of urine/serum urate to urine/serum creatinine at high blood levels of salicylate suggest that the mechanism of hypouricemia is secondary to inhibition of net tubular reabsorption of uric acid from glomerular filtrate.* It should be noticed that

^{*} An alternative explanation for the depression of uric acid is that the high levels of salicylate inhibited the activity of the enzyme uricase used in the determination of uric acid. Therefore, urate recovery experiments were performed on serum with sodium salicylate concentrations of 90 mg. per cent. The data obtained did not differ significantly from control serums within a standard error of ± 3 per cent.

TABLE V
THE EFFECT OF SALICYLATES ON THE RENAL EXCRETION OF URIC ACID
AND SERUM URIC ACID LEVELS

Day	Serum uric acid	Urine(Uric acid conc.) / Urine (Creatinine conc.)	Serum Salicylate
Day	(mg.%)	Plasma (Uric acid conc.) / Plasma (Creatinine conc.)	Level (mg. %)
1	0.13	0.87	80
2	0.53	0.47	21
3	1.36	0.33	20
4	2.54	0.08	23
5	3.14	0.03	3
6	3.50	0.10	0
7	3.35	0.10	0
Normal	3.5-4.5	0.06-0.10	0

on hospital days two, three and four, total salicylates remained approximately constant while the uric acid excretion fell from 47 to 8 per cent of the filtered load. Since these data are based on total and not free salicylates, they suggest that the conjugated salicylates are not effective in inhibiting net uric acid transport. This agrees with the findings of Schachter and Manis [29].

The depression of serum uric acid may be of more than academic interest. In patients in whom the diagnosis of salicylate intoxication is difficult, hypouricemia may be regarded as a finding favoring this diagnosis.

Transient albuminuria and red cells and casts during intoxication have been reported previously. Case vi (J. D.), as previously mentioned, has been reported by Campbell and Maclaurin as an example of acute renal failure in the diuretic phase produced by salicylate intoxication.

Bywaters and Joekes [37], Bracey [38], and Miller [39] have also reported examples of salicylate intoxication in which azotemia and renal failure were prominent features. Renal failure occurs only rarely, usually being a late complication of severe intoxication and may be secondary to prerenal factors impairing glomerular filtration rate.

Central nervous system manifestations, in addition to those involving the respiratory center, are common. Drowsiness, dementia, or frank coma were present in all six patients reported here. The mechanism of these central nervous system manifestations is not known.

It is generally accepted that the mechanisms of death from salicylate intoxication include central nervous system depression, respiratory arrest, or cardiovascular collapse. It is possible that some deaths from salicylate intoxication may occur as a result of hypokalemia. No data are available, however, to substantiate this possibility. No patient in the present series died.

SUMMARY

The case histories of six patients with severe salicylate intoxication are presented. The features of this disorder are discussed in the light of these case histories. The initial effect of salicylates on acid-base balance is the production of respiratory alkalosis. The basis for the respiratory alkalosis is a direct central effect which requires the anterior hypothalamus for its mediation. One of the important results of this respiratory alkalosis is hypokalemia. The hypokalemia is manifested by low serum potassium concentrations, electrocardiographic and neuromuscular changes. The persistence of hypokalemia when alkalosis is no longer present indicates that potassium depletion is likewise present. The manifestations of hypokalemia and potassium depletion may be reversed by adequate potassium therapy. Other consequences of the respiratory alkalosis may include tetany and interference with tissue oxygenation. Therapy for this phase of the disease include fluid replacement, potassium replacement, and oxygen. The use of alkali and of respiratory center depressants is contraindicated.

Some patients with severe salicylate intoxication may develop metabolic acidosis following the stage of respiratory alkalosis. The manifestations of the respiratory alkalosis and metabolic acidosis are so similar that frequent blood pH measurements are necessary to guide therapy. This is particularly true because the disease may progress from one stage to the other without obvious change in the patient's status. The most important therapeutic agent for metabolic acidosis is the administration of sodium bicarbonate or lactate.

Other important effects of salicylate intoxication include: fever, hypoprothrombinemia, hemorrhagic gastritis, hypermetabolism, hypouricemia, renal failure, delirium, coma, and ultimately central nervous system depression. The prognosis of the adequately treated patient would appear to be good.

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Pheochromocytoma Associated with Multiple Neurofibromatosis and Intracranial Hemangioma*

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F diagnosed with much greater frequency in recent years because of the rapid increase in our knowledge of the clinical and pharmacological characteristics of the tumor. One of the most interesting and practical clinical observations is the tendency of this lesion to occur in patients who have multiple neurofibromatosis (von Recklinghausen's disease). In 1953 Glushien et al. [1] reviewed the reported cases of this association of lesions, and described a case of their own. In addition, they reported on two patients with pheochromocytoma who also had angiomatosis retinae (von Hippel's disease), and pointed out the similarity of this disorder to neurofibromatosis and the other neurocutaneous syndromes.

It is the purpose of this paper to describe three additional cases of functioning pheochromocytoma in patients with neurofibromatosis diagnosed antemortem and successfully treated surgically. Two cases of pheochromocytoma associated with intracranial hemangioma are also described and an attempt is made to fit them into the spectrum of the neurocutaneous syndromes.

CASE REPORTS

CASE I. J. L. (MCV B235929), a thirty-six year old Negro woman, was admitted to the hospital on October 2, 1957, with a sixteen-month history of episodes of sweating, headache, nervousness, palpitation, and nausea and vomiting. Her physician had

found her blood pressure to be 200/150 mm. Hg during an episode. Generalized neurofibromatosis had been confirmed by biopsy during a previous hospital admission.

Pertinent physical findings included a blood pressure of 170/120 mm. Hg and a pulse of 120 per minute. Extensive neurofibromas were present, as were café au lait spots. Grade 3 hypertensive retinopathy was noted. Examination of the heart revealed no abnormalities. The fasting blood sugar was 174 mg. per cent and the basal metabolic rate plus 40 per cent. The cold pressor test resulted in a blood pressure rise from 165/130 to 210/150 mm. Hg. On intravenous injection of 0.025 mg. of histamine base the blood pressure rose from 170/135 to 300/220 mm. Hg, and this was associated with marked headache, diaphoresis, palpitation and abdominal pain. When the blood pressure failed to decline after two minutes, 5 mg. of phentolamine (Regitine®) was injected intravenously following which the blood pressure dropped to 120/100 mm. Hg. Blood catechol amines drawn immediately before and four minutes following the histamine injection were reported as follows:

	Epinephrine†	Norepinephrine
Before histamine After histamine Normal range	3.9 μg./L. 23.9 μg./L. 0.6 to 2.0 μg./L.	6.1 μg./L. 14.9 μg./L. <9.0 μg./L.

†We are indebted to the Laboratory for Surgical Research at the Medical College of Virginia under the direction of Dr. David M. Hume for these determinations. The blood catechol amines were determined by a modification of the method of Weil-Malherbe and Bone [2].

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Intravenous injection of 14.8 mg. of piperoxan (Benodaine®) resulted in a fall in blood pressure from 165/125 to 140/100 mm. Hg. An intravenous phentolamine test caused a drop from 170/125 to 120/80 mm. Hg. Estimation of urinary catechol amines revealed a twenty-four-hour excretion of $6,000~\mu g.$, calculated as epinephrine.* By the method of von Euler [3], on another day the twenty-four-hour excretion of epinephrine was $716~\mu g.$ and of norepinephrine $268~\mu g.$ † Normal values in this laboratory are less than $30~\mu g.$ of norepinephrine and less than $20~\mu g.$ of epinephrine per twenty-four-hours. An intravenous urogram failed to localize the tumor.

Laparotomy revealed a benign pheochromocytoma involving the left adrenal gland. The tumor measured 11.5 by 8 by 4 cm. and weighed 210 gm. A total of 35 mg. of phentolamine was utilized to combat marked blood pressure rises prior to excision of the tumor. Following extirpation of the tumor a fall in systolic blood pressure to 90 mm. Hg was easily controlled with infusions of norepinephrine and phenylephrine. Several days postoperatively an episode of atrial tachycardia associated with an unobtainable blood pressure occurred but responded to rapid

digitalization.

Four months postoperatively the patient was readmitted for study. She was asymptomatic and normotensive, and had gained 20 pounds. The appearance of the optic fundi had returned to normal. The fasting blood sugar was 85 mg. per cent and the basal metabolic rate was -14 per cent. Results of a histamine test were negative. Estimation of urinary catechol amines by the method of von Euler revealed a twenty-four-hour excretion of 15 μ g. assayed as norepinephrine and 2 μ g. of epinephrine. Blood catechol amines before and four minutes after histamine were reported as follows:

	Epinephrine	Norepinephrine
Before histamine	0.5 μg./L. 0.01 μg./L.	0.6 μg./L. 0.4 μg./L.

The clinical picture of a marked hypermetabolic state with tachycardia, diabetes and increased basal metabolic rate suggested a predominantly epinephrine-secreting tumor. The catechol amine values confirmed this impression. The high levels of epinephrine also suggested that the tumor was in the vicinity of the adrenal medulla, as emphasized by von Euler and Ström [4].

CASE II. E. R. (MCV A067675), a thirty-one year old Negro woman, was admitted to the hospital on June 22, 1953, because of episodes of nervousness, palpitation and headache of four months' duration. She was a frequent visitor to the outpatient department, and the abrupt onset of her hypertension four months prior to admission could be well documented. Biopsy of a nodule on her right thigh had been performed elsewhere and found to be a neurofibroma.

Examination revealed a blood pressure of 220/120 mm. Hg and a pulse of 100 per minute. Segmental narrowing of the retinal arterioles was noted. Numerous café au lait spots and neurofibromas were present.

The fasting blood sugar was 123 mg. per cent and the glucose tolerance test was diabetic in type. The basal metabolic rate was plus 31 per cent. Following intravenous injection of 5 mg. of phentolamine the blood pressure dropped from 160/105 to 115/70 mm. Hg. A blood pressure rise from 170/110 to 285/150 mm. Hg followed the intravenous injection of only 0.01 mg. of histamine base. A decline in blood pressure of 25/20 mm. Hg followed intravenous injection of 14.6 mg. of piperoxan. A presacral oxygen study for visualization of the adrenals showed a right-sided suprarenal mass.

Laparotomy revealed a pheochromocytoma of the right adrenal measuring 5.5 by 3.5 cm. During surgery excessive blood pressure rises were controlled by intravenous phentolamine. A fall in blood pressure to 90/60 mm. Hg following removal of the tumor responded to an infusion of norepinephrine. Three years postoperatively the patient remained normo-

tensive and asymptomatic.

CASE III. M. G. (MCV B136243), a forty-nine year old white woman, was admitted to the hospital on March 24, 1952, for evaluation of severe headaches of seven years' duration. At the age of forty-two, while pregnant, she was hospitalized briefly because of hypertension. She gave a history of generalized neurofibromatosis since the age of eighteen and her father, a paternal uncle, and four sisters have the same disorder. Heat intolerance, nervousness and palpitation occurring in episodes were prominent symptoms.

Physical examination revealed a blood pressure of 180/110 mm. Hg and a pulse of 100 per minute. Multiple pedunculated neurofibromas and café au lait spots were present. Mild hypertensive retinopathy was noted. Examination of the heart was normal.

The basal metabolic rate was plus 78 per cent, and the fasting blood sugar was 127 mg. per cent. Following administration of 5 mg. of phentolamine the blood pressure dropped from 250/120 to 160/80 mm. Hg. After injection of 0.03 mg. of histamine base intravenously the blood pressure rose from 180/100 to 245/120 mm. Hg. The cold pressor test produced no rise in the blood pressure. A drop in blood pressure of 66/44 mm. Hg followed injection of 13 mg. of piperoxan and was associated with marked dyspnea.

^{*} Performed by the Boston Medical Laboratory using the fluorometric method of Goldenberg in which normal values are less than 100 μ g./L.

[†] See footnote under table on preceding page.

No presacral oxygen study for visualization of the adrenals was made. The twenty-four-hour excretion of catechol amines was 880 μ g. per twenty-four hours, assayed as norepinephrine* by the method of Goldenberg [5].

Abdominal exploration revealed a 5 by 4 cm. pheochromocytoma of the right adrenal gland. Three excessive blood pressure rises required intravenous phentolamine, and a norepinephrine infusion was required for twenty-four hours postoperatively to control the hypotension. The tumor weighed 43 gm. It was assayed for catechol amines and contained 0.42 mg. of epinephrine per gm. and 5.1 mg. of norepinephrine per gm.* The patient made an uneventful recovery. Four years postoperatively she was found to be asymptomatic, and the histamine test was negative.

These cases represent three previously unreported patients who had neurofibromatosis associated with pheochromocytoma.

Case IV. A. H. (MCV B25001), a fifty-five year old white woman, was admitted to the hospital on May 26, 1947, shortly after having been struck by an automobile.

The past history revealed that she had previously been admitted to the hospital on several occasions from 1931 to 1940 because of bilateral optic atrophy and headaches. In 1936, because of an enlarged sella turcica, a right frontal craniotomy was performed but no lesion was found. Biopsysof a subcutaneous nodule at that time revealed a neurofibroma. In 1940 she complained of episodes of marked nervousness, headache and weakness. Her blood pressure was recorded as 170/100 mm. Hg at that time.

Physical examination, in addition to multiple traumatic fractures, revealed many neurofibromas and café au lait spots. Her blood pressure was 210/150 mm. Hg.

Eight hours after admission it was noted that she was having marked fluctuations in blood pressure. Shortly afterward profound circulatory collapse developed, she became comatose and died.

Examination of the brain at autopsy revealed the lateral and third ventricles to be markedly dilated. A large hemorrhagic tumor mass, 2 by 3 cm., was present in the fourth ventricle arising from the ventral surface of the cerebellum and obstructing the foramina of Magendie and Luschka. Microscopically the lesion was composed of masses of thin-walled vessels with very little interstitial tissue. A pheochromocytoma weighing 260 gm. was found lying within the capsule of the left kidney, the adrenal being adherent to its

* We are indebted to Dr. Marcel Goldenberg of the College of Physicians and Surgeons, Columbia University, for these determinations. Paper partition chromatography and a modification of the fluorometric method of von Euler were utilized for the tumor assay.

surface. Multiple fractures were present, as were fat emboli in the pulmonary vessels.

This patient, previously reported on [6,7], presents the triad of neurofibromatosis, cerebellar hemangioma and pheochromocytoma. Her symptoms suggested that the tumor was functioning, although her death occurred prior to the advent of currently used diagnostic tests.

The following patient, we believe, represents the fourth reported case of pheochromocytoma associated with the von Hippel-Lindau syndrome.

Case v. L. S. (MCV B172356), a twenty-four year old white woman, was admitted to the hospital on July 31, 1953, because of coma of two hours' duration. She was nine months pregnant at the time. Her pregnancy had been normal throughout until June 12 when her blood pressure was found to be 130/90 mm. Hg. Subsequent blood pressures were all mildly elevated, the highest recording being 140/100 mm. Hg. There were no other findings suggestive of preeclampsia. On the night of admission she complained of severe headache, vomited, and rapidly became unconscious.

Physical examination revealed a deeply comatose white woman. No neurofibromas or café au lait spots were present. Her blood pressure was 160/80 mm. Hg, her pulse 140 per minute, and her temperature 104.2° F. Her pupils were pinpoint and failed to respond to light. The fundi, unfortunately, could not be adequately visualized due to the small pupils. The neck was stiff. Examination of the heart and lungs was within normal limits. The abdomen was enlarged to the size of a term pregnancy, and the fetal heart tones were audible in the left lower quadrant. The deep tendon reflexes were absent, and there was no response to plantar stimulation.

Lumbar puncture revealed a grossly bloody spinal fluid with an opening pressure of 300 mm. of water. The blood sugar was 116 mg. per cent, and the blood urea nitrogen 12 mg. per cent. The hemoglobin was 14.4 gm. per cent.

The patient remained comatose and died two hours following admission. The fetal heart sounds became inaudible forty minutes to her death.

At autopsy there was extensive subarachnoid and intraventricular hemorrhage. Three small capillary hemangiomas of the medulla were present, one of which was ruptured. The right adrenal gland weighed 61 gm. and was the site of a pheochromocytoma.

Perhaps the most interesting aspect of this patient's case is her unusual family history, which has been made available to us by Dr. David B. Clark of Baltimore. According to his information, the patient's mother died at the age of thirty-six, in another city, of tuberculous meningitis. At autopsy a "cystic lesion" of the cerebellum was described by the prosector although no microscopic sections were made. Our pa-

tient's grandfather died following paralysis of both lower extremities which was attributed to a fall from a horse. However, the onset of neurological symptoms did not follow the accident immediately but occurred after some unknown period of time. Our patient's father was said to have had two large brown pigmented spots on his legs. Several members of his family were known to have had neurofibromatosis. Our patient's sister has recently been studied at another institution where she was found to have angiomatosis retinae for which she has been treated surgically. In addition, she is being followed up for progressive neurological changes, which are considered to be due to a posterior fossa lesion. She has a small café au lait spot on her hand and her small daughter has several similar pigmented spots.

It is impossible to know definitely whether L. S. had pre-eclampsia or if her mild hypertension represented the onset of function of the pheochromocytoma

found at autopsy.

The cystic lesion of the cerebellum noted at her mother's autopsy might have been a cystic hemangioblastoma. Similarly, her maternal grandfather's spinal cord lesion conceivably could have been due to a hemangioma rather than to trauma. Thus these patients may have had von Hippel-Lindau's disease although proof is lacking. There is a more definite history of neurofibromatosis on the paternal side of the family. Our patient's sister, who has von Hippel's disease and probably Lindau's disease also, has a pigmented lesion often seen in neurofibromatosis. The occurrence of multiple café au lait spots on our patient's niece suggests that she may represent an incomplete form of the syndrome.

COMMENTS

Tuberous sclerosis, multiple neurofibromatosis, von Hippel-Lindau's disease and the Sturge-Weber syndrome have been grouped together and classified as the neurocutaneous syndromes by many authors [8-13]. Van der Hoeve [12] proposed the name phakomatoses for these disorders, the name being derived from the Greek word phakos or mother spot. There is a great deal of evidence to suggest that these disorders are in some manner related. The major abnormalities involve the structures of ectodermal origin. They are all congenital and may be heredofamilial. Two or more of these diseases have occurred in one patient [10] as well as in members of the same family [8]. Although the clinical manifestations of these syndromes are extremely variable, the most common abnormalities found in each can be briefly reviewed.

Multiple neurofibromatosis is a disease which

is characterized by cutaneous pigmentation (brown spots of variable size), skin lesions (vascular naevi, hairy moles and polyps) and multiple tumors of the nervous system. The latter consist of neurofibromas of the peripheral nerves which may appear as flat or pedunculated subcutaneous nodules or as plexiform neuromas. In addition, meningiomas and gliomas may involve the nervous system. Many of the lesions are highly vascular and distinct vascular anomalies have been described [6,8,14]. These blood vessel malformations tend to link neurofibromatosis to the Sturge-Weber syndrome and von Hippel-Lindau's disease. Retinal tumors have also been described which are primarily gliomatous but are often quite vascular as well. This led Van der Hoeve [12] to compare them to von Hippel's disease.

Tuberous sclerosis is characterized by the triad of recurrent seizures, mental deficiency, and multiple facial naevi. These latter lesions are termed adenoma sebaceum. Multiple neurofibromatosis may also occur either in these patients or in members of the same family [8,11, 14,15]. Pathologically, gliomatous nodules are found throughout the substance of the brain and frequently in the walls of the ventricles. Retinal tumors called phakomas may be found. They consist of glial and ganglion cells and small blood vessels [8,15] and may simulate von Hippel's disease [15]. Greig [16] in 1922 reported a patient with tuberous sclerosis who had a large vascular malformation over the left cerebral hemisphere. This case serves to link tuberous sclerosis with the Sturge-Weber syndrome. Finally, congenital cysts of the pancreas and kidney and atypical hypernephromas may occur.

The Sturge-Weber syndrome (encephalotrigeminal angiomatosis) consists of hemangiomas of the face, particularly over the distribution of a division of the trigeminal nerve, angiomatous involvement of the meninges and brain, and seizures which are often jacksonian in type. The cutaneous and cerebral angiomas are frequently in a corresponding area. Buphthalmos and

hemiplegia may occur.

Von Hippel's disease (angiomatosis retinae) [17] consists of one or more angiomatous malformations of the retina, each supplied by a dilated artery and vein. The lesion progresses to form hemorrhages and exudates and finally retinal detachment may occur [15]. Secondary glaucoma may necessitate enucleation. In approximately 20 per cent of these patients signs

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of intracranial tumor develop [9]. Lindau [18,19] found that the typical lesion of the central nervous system associated with angiomatosis retinae was a cystic hemangioblastoma which involved the cerebellum. Other portions of the brain and spinal cord were sometimes involved and solid hemangiomas occurred as well. Not infrequently cystic lesions of the pancreas and kidney were found, as were hypernephromas. The visceral lesions are very similar to those seen with tuberous sclerosis.

It is not surprising that the neurocutaneous syndromes and pheochromocytomas should occur together, since embryologically the major abnormalities occur in tissues derived from a single germ layer, the primitive ectoderm. During the fourth embryonic week the neural plate, which has formed as a thickening of a portion of the ectoderm, invaginates, fuses, and forms the neural tube [20]. In this manner the primitive central nervous system is separated from the skin. The chromaffin cells of the adrenal medulla arise from the primitive neural crest [21] and invade the primordial cortical mass during the seventh fetal week. Finally, the retina is formed by the fusion of the two layers of the optic cup which is an evagination of the forebrain. Thus a dysplasia or malformation of the neurectoderm, as some authors believe these disorders to be [9-11], would be likely to produce lesions at any of these sites. However, this concept is confused by the occurrence of renal and pancreatic cysts and hypernephromas which are structures of mesodermal origin.

The association of pheochromocytoma with multiple neurofibromatosis has been described in thirty-two previous cases. Glushien et al. [1] in 1953, in an extensive review of the literature, found eighteen cases including their own. We have been able to find fourteen additional cases in the literature since 1952. These are listed in Table 1. Since our patient, A. H., was included in the cases of Glushien et al., the present series increases the total number of published cases to thirty-five.

Three patients reported by Braley [36] in 1954 were omitted from Table 1 because their findings were not extensive enough to permit classification as definite cases of neurofibromatosis. They had pheochromocytomas, plexiform neuromas of the eyelids and myelinated corneal nerve fibers. Neurofibromas of the lids, however, have been described as the only finding in abortive cases of von Recklinghausen's disease [11] and mye-

Table 1
PHEOCHROMOCYTOMA WITH NEUROFIBROMATOSIS—
CASE REPORTS SINCE 1952

Author and Year	Age (yr.) and Sex	Site of Tumor
Koonce et al. [22] 1952	50, M	Both adrenals
Hamilton et al. [23] 1953	66, F	Right adrenal
Minno et al. [24] 1954	46, F	Right adrenal
Snyder and Rutledge [25] 1955	13, M	Right adrenal
Riishede [26] 1955	26, F	Right adrenal
Knox and Slessor [27] 1955	40, M	Left adrenal
Morrison et al. [28] 1956	32, M	Right adrenal
Steen [29] 1957	47, M	Right adrenal
Killins and Eberbach [30]	11, 212	reight marchar
1957	45, F	Left adrenal
Boldt et al. [31] 1957	56, F	Right adrenal
Unger [32] 1957	30, F	Not stated
Healey and Mekelatos [33]	50, 2	
1958	25, M	Left adrenal
Lopez [34] 1958	38, F	Left adrenal
Schröder [35] 1958	28, M	Right adrenal
Present authors:	,	0
Case 1	36, F	Left adrenal
Case II	39, F	Right adrenal
Case III	49, F	Right adrenal

linated corneal nerve fibers have been recorded in patients with classical neurofibromatosis.

The incidence of neurofibromatosis in large series of cases of pheochromocytoma is generally said to be 5 to 10 per cent [33,37], although Cahill and Monteith [38] found an incidence of 20 per cent. The total number of pheochromocytomas on record at our clinic is sixteen, including functioning and non-functioning tumors and those found at autopsy. The occurrence of neurofibromatosis in four patients makes our incidence 25 per cent, which is considerably higher than the figures cited.

A review of the records of cases of proved neurofibromatosis observed at our clinic in the past ten years was made in order to determine the incidence of pheochromocytoma in neurofibromatosis, and possibly to uncover previously unsuspected cases which might be present in our records. The charts of thirty patients with neurofibromatosis were reviewed but no cases particularly suggestive of pheochromocytoma were found. One patient, the son of patient M. G., had very suggestive symptoms but was never noted to be hypertensive. Repeated studies with histamine, injected intravenously, have failed to show any evidence of functioning pheo-

chromocytoma. In our small series of thirty patients with neurofibromatosis the incidence of

pheochromocytoma was 13 per cent.

A rather striking preponderance of left-sided pheochromocytomas was noted by Glushien et al. [1] in their series of eighteen patients. There were thirteen left-sided tumors, only three right-sided tumors, and bilateral involvement of the adrenals in two patients. Since the right adrenal gland is the site of 60 per cent of pheochromocytomas in patients not having neurofibromatosis, this was thought to be a significant finding and it was suggested that the left adrenal should be explored first when neurofibromatosis was present. However, it is apparent from Table I that since their report right-sided tumors have been found twice as often as left-sided ones. When the two series are combined it is noted that left-sided pheochromocytomas have been reported in eighteen patients, right-sided ones in thirteen patients, and bilateral tumors in three instances. Thus it would appear that the tendency of pheochromocytomas to occur on the left in patients with neurofibromatosis is not nearly so striking as was initially believed.

Glushien et al. [1] were the first to suggest an association between pheochromocytoma and von Hippel-Lindau's disease. In 1953 they reported two patients with pheochromocytoma and angiomatosis retinae. One of these patients who died had shown no evidence during life of hemangioma in the central nervous system, and at autopsy the brain was not examined. The other patient was still living with no symptoms to suggest an intracranial lesion. No mention was made of the patients' family histories.

The same authors reviewed a case reported by Wolf and Wilens [39] who had three paragangliomas of the left adrenal. In addition, multiple hemangioblastomas of the spinal cord, a cystic hemangioblastoma of the cerebellum, congenital cysts of the pancreas and kidneys, a benign hypernephroma and syringomyelia were found at autopsy. Both eyes had previously been enucleated because of retinal detachment. This patient then had a pheochromocytoma and Lindau's disease. He most likely had von Hippel's disease as well, since angiomatosis retinae is said to be bilateral in 50 per cent of patients [40] and retinal detachment and secondary glaucoma requiring enucleation is a common course of events in untreated patients [15]. Thus it would appear that there were two previously published and well documented cases of pheo-

chromocytoma with angiomatosis retinae and one with Lindau's disease who probably also had angiomatosis retinae as well. Glushien et al. [1] also reviewed two cases in which the association of von Hippel-Lindau's disease with pheochromocytoma was suggested, but sufficient information to make a definite diagnosis was lacking. The first case was that of Harbetz [41] whose patient at autopsy had two paragangliomas, multiple cysts of the pancreas, and a malignant hypernephroma with widespread metastases. No clinical information was given and no mention was made of the brain or eyes. The second case was that of Sellas [42] who described a patient with angiomatosis retinae who was prone to have "attacks of hypertension." This patient died at an early age but no autopsy was performed. Finally, it is interesting to note that one of Lindau's original patients [19] with cerebellar angiomas was found to have bilateral adrenal tumors at autospy. Unfortunately the nature of these lesions was not clarified.

Since patient A. H. had no family history of von Hippel-Lindau's disease and since she had typical neurofibromatosis, it seems best to consider her cerebellar hemangioma to be a manifestation of the latter disorder. Patient L. S. is more difficult to categorize. There was a definite family history of both von Hippel-Lindau's disease and neurofibromatosis in her family, but she had no lesions typical of the latter. The multiple capillary hemangiomas of the medulla in this case are more suggestive of Lindau's disease since Lindau [18,19] pointed out that these lesions occurred as part of the syndrome. It is also well known that incomplete forms of the disorder may occur [15]; therefore, it seems most likely that this case represents an abortive form of Lindau's disease.

Whether or not our last patient is considered to have Lindau's disease it appears that the association of pheochromocytoma with this disease has been reported too often to be coincidental. This points up the importance of considering the presence of such a tumor when a patient with von Hippel-Lindau's disease has symptoms of pheochromocytoma and/or hypertension.

SUMMARY

1. Three additional patients with pheochromocytoma associated with multiple neurofibromatosis are reported. A review of the literature since 1952 revealed fourteen additional cases of this association of lesions. This brings the total

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number of cases known to the authors to thirty-five.

2. A patient with pheochromocytoma, neurofibromatosis and a cerebellar hemangioma, previously reported from this institution, is described again in the light of present information.

3. A patient with pheochromocytoma, multiple brain stem hemangiomas, and a family history of both von Hippel-Lindau's disease and multiple neurofibromatosis is reported. The previously reported cases in which pheochromocytoma has been associated with von Hippel-Lindau's disease are reviewed.

4. The striking similarity of the various neurocutaneous syndromes is re-emphasized and an attempt is made to explain this relationship on an embryological basis. The occurrence of pheochromocytoma in these patients can also be accounted for by this hypothesis.

5. It is concluded that the association of these familial disorders of the neurectoderm with pheochromocytoma is not only helpful in the clinical diagnosis of pheochromocytoma, but strengthens the concept that they are all related disorders of those structures of ectodermal origin.

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Studies in Disorders of Muscle*

XII. Myopathy Due to the Administration of Therapeutic Amounts of 17-Hydroxycorticosteroids

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MUSCULAR weakness is a common finding in hyperadrenocorticism. When Cushing described the clinical features of this disorder [1] he noted that weakness was present in half of his patients. Twenty years later Plotz et al. [2] found a similar incidence in a review of 189 cases of Cushing's syndrome collected from the literature. The incidence in their own thirty-three cases was 83 per cent.

The current widespread use of adrenocortical hormones for the treatment of a variety of disorders has led to the production of Cushing's

orders has led to the production of Cushing's syndrome in patients receiving these agents. Under these circumstances the occurrence of hyperadrenocorticism represents a side effect of therapy. Although muscular weakness has been reported to be one of the untoward effects of steroid therapy [3,4], its importance has been overshadowed by other aspects of hyperadrenocorticism. Thus the clinical features of the muscle disorder associated with spontaneous or induced Cushing's syndrome have not been described in detail and little information is available concerning the histology of muscle during adrenal hor-

mone therapy.

We have observed severe muscular weakness associated with muscle atrophy in seven patients treated with adrenal steroids over the last five years. In some of these patients complete incapacitation, comparable to Cushing's original patient who was "unable to hold a pencil from weakness" [1], resulted from therapy. It is the purpose of this report to call attention to the

importance of this side effect of steroid hormone therapy and to describe the clinical, laboratory and histologic findings associated with it.

CLINICAL MATERIAL

The seven patients described in this paper had been referred to the Salt Lake County General Hospital for the diagnosis and treatment of hematologic disorders. Except for Case II, urinary and/or serum creatine and creatinine were measured in each case. During the urine collection periods, patients 1, 4, 5 and 6 consumed creatine-free diets. Patients 3 and 7 ate normal diets. All patients received supplementary potassium chloride (1 gm. three times a day) whenever cortisone was given.

For comparison with the patients in whom muscle weakness developed secondary to steroid therapy, representative observations of creatine and creatinine excretion by persons given adrenocorticotrophic hormone are included in this paper. This group of patients includes six with various forms of progressive muscular dystrophy, three with chronic rheumatoid arthritis and one each with interstitial cystitis and acute leukemia. Similar studies were made in one patient with severe, acute dermatomyositis who was treated with prednisone.

METHODS

Urine and serum creatine and creatinine were determined by a modification of the method of Phillips [5]. Serum sodium and potassium levels were measured with a Beckman flame photometer. Biopsy of the quadriceps femoris muscle was performed in three patients. In one of these, muscle also was obtained later at autopsy. Muscle sections were likewise available from the autopsy of a fourth patient.

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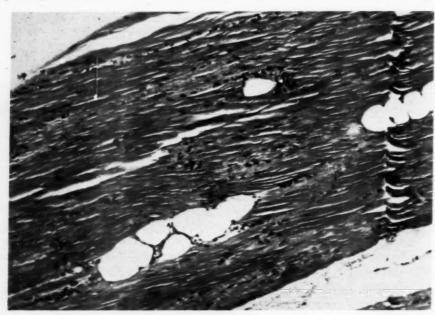


Fig. 1. Photomicrograph of the muscle biopsy specimen in Case I. Vacuoles seen in other specimens were smaller than these, but were similar in all other respects.

CASE REPORTS

Case I. M. O., a white housewife, fifty-two years of age, was found to have hemolytic anemia secondary to lymphosarcoma. Laboratory examinations revealed the volume of packed red cells to be 10 per cent; white blood cell count, 5,200 per cu. mm.; serum bilirubin, 0.5 mg. per 100 ml. direct, 1.6 mg. per 100 ml. total. Bone marrow aspiration revealed 56 per cent lymphocytes.

Cortisone therapy (300 mg. daily) was initiated. In the course of the following twenty months the dose of cortisone required to control the hemolytic process ranged between 100 and 200 mg. daily. In April 1954 therapy was changed to prednisone, 60 to 80 mg. daily. At that time the patient first noted some difficulty in climbing stairs. Two weeks later the weakness in the lower extremities had progressed so that she would collapse on the floor when her "legs gave way" in attempting to walk.

Physical examination revealed an obese woman with a cervicodorsal fat pad. There was weakness and atrophy of the flexor and extensor muscles of the hip. The motor power of the quadriceps femoris muscle was diminished and the patient was unable to rise from a sitting or kneeling position. In addition, there was slight weakness of the musculature of the shoulder girdle. The remainder of the neurological examination was normal.

The quadriceps muscle was biopsied while the patient was receiving prednisone, 80 mg. per day. Histologic examination revealed normal cross striation. There was no increase in sarcolemmal nuclei and no cellular infiltrate or excess of fat or fibrous tissue. Several medium-sized, clear intracellular vacuoles were found. These are shown in Figure 1. Steroid

therapy was continued until the patients death, which was due to terminal pyelonephritis and Escherichia coli septicemia. At autopsy, the rectus abdominus muscle was sectioned. No abnormalities could be demonstrated in this muscle at that time. There were no vacuoles. Nerve stains and periodic acid-Schiff stain were normal.

CASE II. J. R. M. was a three year old girl who was found to have acute leukemia. Three months after the first symptoms of the disease had appeared cortisone therapy (100 mg. daily) was begun. After six weeks remission ensued and cortisone therapy was discontinued. Eleven months later, when relapse had occurred, cortisone therapy (150 mg. daily) was restarted. After three weeks of treatment the patient noted difficulty in arising from a lying or sitting position unless she used her hands to raise herself. Physical examination demonstrated the presence of a round, plethoric face, a cervicodorsal fat pad, and pedal edema. Weakness was confined to the pelvic and gluteal musculature. On arising from a sitting position she found it necessary to brace her hands on the legs, pushing herself to an erect position (Gower's maneuver). The deep tendon reflexes were normal. Cortisone was discontinued and two weeks later these symptoms and signs were markedly improved, despite progression of the leukemia. Death occurred twenty-one months after the first evidence of the disease had been

Sections of the quadriceps femoris and psoas muscles were available for study. Most of the muscle fibers were normal. Some of the fibers, however, showed a distinct increase in the number of sarcolemmal nuclei. Clear vacuoles which contained only granular debris were present in a few scattered fibers

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and one fiber demonstrated total vacuolization. The peripheral nerves were normal.

Case III. L. B. was a ten year old boy who was found to have acute leukemia. Laboratory examination revealed a hemoglobin of 7 gm. per 100 ml. The white blood cell count was 4,000 per cu. mm. and the differential count included 64 per cent lymphoblasts.

In the course of the following twenty months of his illness the patient was treated successively with prednisone, 6-mercaptopurine and amethopterin. The last course of prednisone (40 mg. daily) was started twenty-one months after the diagnosis was first made. As had happened previously during the administration of this hormone, a markedly rounded face and large supraclavicular and cervicodorsal fat pads developed in the boy. His abdomen became protuberant and purple striae appeared. Two months later he complained of weakness and aching of the thigh and calf muscles. On physical examination there was atrophy of the quadriceps femoris muscle and of the calf muscles. Motor power of the flexor and extensor muscles of the hip was diminished. The upper extremities did not appear atrophic. No other neurologic abnormalities were noted.

Case IV. R. M. was a thirty-two year old man who was found to have acute acquired hemolytic anemia. Splenectomy had been performed. Nevertheless, when he was first seen by us three months later, severe anemia was still present. The volume of packed red cells was 21 per cent; white blood cell count, 23,200 per cu. mm. with a differential count of lymphocytes 35 per cent; polymorphonuclear leukocytes, 55 per cent; monocytes, 2 per cent; juvenile forms, 4 per cent; and myelocytes, 4 per cent. Numerous nucleated red blood cells were present in the smear. There was striking anisocytosis, poikilocytosis, polychromatophilia and spherocytosis. The Coombs' test was positive. The serum bilirubin was 0.8 mg. per 100 ml. direct, 2.4 mg. per 100 ml. total.

Cortisone, 400 mg. daily, was prescribed. The anemia was relieved but maintenance of the remission required continuation of cortisone therapy at an average dose level of 250 mg. per day. After a year of such treatment the patient noted inability to rise from a squatting position unless he used his hands to raise himself. Physical examination revealed a round, plethoric face and prominent dorsal and supraclavicular fat pads. The abdomen was protuberant and numerous purple striae were present. In contrast to the patient's corpulent trunk, the extremities were thin and showed evidence of muscle wasting. Muscle atrophy was more marked in the right than in the left thigh. The flexor and extensor muscles of the hip were weak

A quadriceps muscle biopsy was performed while the patient was receiving cortisone, 250 mg. daily. The muscle fibers showed normal cross-striation. There was no fibrous or fatty infiltration and no increase in inflammatory cells. Some of the muscle fibers were smaller than normal and contained increased numbers of sarcolemmal nuclei. A few clear vacuoles were found to be located within individual fibers. These were scattered throughout the section in a random fashion and, except for minute amounts of granular debris, they were apparently empty. Some of the vacuoles appeared to be lined by cells resembling endothelium; others were apparently unlined.

It has since become possible to maintain this patient on smaller doses of hormone, namely 20 mg. prednisone daily. Muscle weakness and atrophy are no longer present.

CASE V. R. S. was a forty-five year old housewife who was found to have acquired hemolytic anemia. When the patient was first seen at this hospital she had been taking prednisone, in a dose of 60 mg. daily, for two months. She was obese, pale, but slightly jaundiced, and had a rounded face. No muscular weakness or atrophy was noted. The volume of packed red cells was 25 per cent. There was marked anisocytosis, poikilocytosis, spherocytosis and polychromatophilia. The Coombs' test was positive. After the diagnosis of acquired hemolytic anemia was confirmed, the dose of prednisone was increased to 100 mg. daily. One month later the patient noted weakness in the lower extremities and difficulty in walking. She found that she would collapse on the floor because her "legs gave way." So long as the dose of prednisone was maintained at 100 mg. daily her weakness became progressively more severe. The patient's muscular strength waned to the point where she was unable to rise from the sitting position without assistance. Atrophy of the musculature of the lower extremities was striking. (Fig. 2.) There was bilateral weakness of the flexors and extensors of the thigh and of the peroneal and anterior tibial muscle groups. In the upper extremities there was marked atrophy of the biceps, triceps and wrist flexors. The grip was weak and the mass of the hypothenar, thenar and interosseus muscles was decreased. There were no fasciculations. Reflexes were active and equal bilaterally. Coordination and orientation were good. Sensory perception was unimpaired.

A month later, splenectomy was performed and two weeks after the operation the dosage of prednisone was decreased to 40 mg. daily. The symptoms of muscular weakness decreased considerably after three weeks of maintenance on the smaller dose. The patient was able to rise from the sitting position and to walk unassisted. In the ensuing year the anemia improved. The prednisone dosage gradually has been reduced to 7.5 mg. per day. Muscle weakness is no longer present, although modest thigh atrophy persists.

Biopsy of the quadriceps muscle was performed while the patient was receiving prednisone, 100 mg. per twenty-four hours. The majority of the muscle





Fig. 2. Lower extremities, Case v. Note the striking muscle atrophy.

fibers were normal. Cross striation was good. There was no increase in fat or fibrous tissue and no cellular infiltrate was found. Some of the fibers, however, showed an increased number of sarcolemmal nuclei. Intracellular vacuoles were not present.

Case vi. G. F. was a fifty-seven year old widow who had been known to have chronic lymphocytic leukemia for five years. Physical examination revealed obesity and generalized lymphadenopathy. The volume of packed red cells was 29.5 per cent, and the white blood cells, 19,850 per cu. mm., with 90 per cent lymphocytes; the platelet count was 76,000 per cu. mm. Administration of prednisone, 40 mg. per day, was begun on February 30, 1957, and has been continued at an average dose level of 30 mg. per day to the present time. Associated with this therapy the anemia has been relieved.

After three months of treatment facial plethora was noted. The obesity increased. Eleven months after initiation of therapy increasing weakness became prominent, and the patient experienced great difficulty in climbing stairs. Within two weeks she noted decreased size of the legs and thighs. Physical examination revealed severe atrophy of the thighs and legs and less severe atrophy of the forearms. There was marked deep pelvic weakness; the patient could not rise from a squatting position. Neither the weakness nor the creatinuria (Table 1) responded to therapy with mixed tocopherols equivalent to 400 mg. α -tocopherol per day.* These findings have persisted

* Eprolin,® kindly furnished by Mr. R. Tueller, Eli Lilly and Company, Indianapolis, Indiana. to the present time, although some subjective increase in strength has occurred in the past month.

CASE VII. E. G. was a seventeen year old girl with acute leukemia. After a four-month history of easy fatigability and fever, anemia, leukopenia and a hypoplastic marrow with 52 per cent blast forms were found. Prednisone therapy, 40 mg. per day, resulted in a clinical remission in one month. After interval therapy with 6-mercaptopurine, symptoms recurred and prednisone, 40 mg. per day, was restarted. Since a clinical remission was not induced treatment with this agent was discontinued after three weeks. At that time the patient complained of cramps in the hands and feet, and difficulty in arising from a kneeling position. Physical examination showed a cervicodorsal fat pad, obesity and plethora of the face. There was marked deep pelvic weakness, with inability to arise from a sitting position without bracing her hands on her knees. Atrophy was not present. The patient died one month later. Autopsy was not obtained.

CREATINE-CREATININE METABOLISM

Serum and Urine Creatine-Creatinine Levels. The results of the measurements of urinary creatine and creatinine in six of these patients are presented in Table 1. In five of the six patients a reduction in urinary creatinine was found, to a degree compatible with the degree of muscle atrophy. In addition, four of five patients showed increased creatinuria: from 193 to 1,062 mg. creatine were excreted per day (normal for children and adult women less than 100 mg. per day). The fifth patient, R. M., showed only slight reduction in urinary creatinine and minimal creatinuria. In those patients in whom the measurements were made reduced serum creatinine and increased serum creatine levels were present, as expected from the urinary data. In Case VII (E. G.), there was moderate elevation of serum creatine and normal urinary creatine and creatinine. The markedly elevated serum creatine observed in R. M. is difficult to explain and may be the result of a technical error.

Urinary Creatine and Creatinine in Patients Given ACTH or 17-Hydroxycorticosteroids for Other Disorders. The clinical data and changes in creatine and creatinine excretion during ACTH therapy of the one additional patient with acute leukemia, and in the patients with muscular dystrophy, rheumatoid arthritis and chronic interstitial cystitis are summarized in Table II. Also included in the table are similar observations made during prednisone therapy of one patient with subacute dermatomyositis. All patients consumed creatine-free diets during the

TABLE I
CLINICAL DATA AND CREATINE-CREATININE VALUES IN PATIENTS WITH STERIOD MYOPATHY

Serum (mg./100 ml.) Creati- nine Crea- tine Diagnosis				Urinary (mg./24 hr.)		Height	Age (yr.)	Case No. and
		Crea- tine	Creati- nine	Weight (lb.)	(in.)	and Sex	Name	
Lymphosarcoma	2.89	0.48	520	450	122	62	52, F	ı, M. O.
Acute leukemia	1.66	0.67	291	761	73	53	10, M	ш, L. В.
Acquired hemolytic anemia	2.95	0.96	116	1425	151	70	32, M	IV, R. M.
Acquired hemolytic anemia	2.89	0.70	1062	627	153		45, F	v, R. S.
Chronic lymphocytic leuker			193	640	154		57, F	vi, G. F.
Acute leukemia	1.43	1.04	80	758	126		17, F	vn, E. G.

Table II
CLINICAL SUMMARY OF OTHER PATIENTS TREATED WITH ACTH OF PREDNISONE

Patient	Age (yr.)	Diagnosis	Therapeutic Agent	Dose (I.U./day)	Duration of Therapy (days)	Change in Creatine Excretion
D. A.	9	Childhood progressive muscular dystrophy	ACTH intramuscularly	40-50	10 (first course) 20 (second course)	Decreased, increased
R. C.	11	Childhood progressive muscular dystrophy	ACTH intramuscularly	20-40	17	Increased
L. L.	38	Facioscapulohumeral muscular dystrophy	ACTH intramuscularly	70	28	Increased
R. S.	49	Myotonia dystrophica	ACTH intramuscularly	60	6	No change
D. DeB.	48	Myotonia dystrophica	ACTH intramuscularly	60	4 .	Slight increase
L. DeB.	53	Myotonia dystrophica	ACTH intramuscularly	60	7	Slight increase
P. L.	25	Acute leukemia	ACTH intramuscularly	100-25	20	Decreased
J. D.	55	Rheumatoid arthritis	ACTH intramuscularly	40	6	Decreased
I. F.	25	Rheumatoid arthritis	ACTH intramuscularly	40	6	Variable
C. S.	31	Rheumatoid arthritis	ACTH intramuscularly	70	16	Decreased, then variable
М. В.	78	Interstitial cystitis	ACTH intramuscularly	40	10	Slight increase
G. O.	38	Dermatomyositis	Prednisone orally	40 (mg./day)	30	No change

collection periods, and daily twenty-four-hour urine samples were obtained before, during and after ACTH or prednisone treatment.

In the six patients with various types of muscular dystrophy, creatinuria increased during five of seven courses of therapy, did not change in one and decreased in one. In the patients with rheumatoid arthritis, the changes in creatinuria were variable in two patients, but treatment was associated with definite decrease in creatinuria in the third. When a decrease in creatinuria occurred in the arthritic patient it paralleled clinical improvement in the basic disorder. The same was true in the patient with acute leukemia. In the one patient with interstitial cystitis, creatinuria increased slightly. In

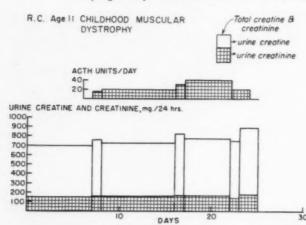


Fig. 3. Urine creatine and creatinine in a patient (R. C.) with childhood muscular dystrophy treated with adreno-corticotrophic hormone.

the patient with dermatomyositis, after one month of therapy with prednisone, 40 mg. per day, no changes in serum or urine creatine had occurred. Because the changes in creatine excretion were variable, only two of the most prominent responses are illustrated in Figures 3 and 4.

COMMENTS

Since weakness is a common finding in patients who have leukemia or hemolytic anemia, the occurrence of this symptom in such patients must be evaluated carefully before it can be ascribed to another cause. In the cases described, however, the complaint was unique in that it often became striking when the patient's underlying disorder was in partial or even complete remission. Furthermore, the pattern of muscular weakness was such as to focus attention especially on the lower extremities; it differed strikingly from the generalized weakness seen in patients with severe anemia. The muscular weakness usually became apparent at the time when other

TABLE III

DOSES OF STEROIDS AND DURATION OF THERAPY BEFORE
ONSET OF SYMPTOMS IN PATIENTS WITH STEROID
MYOPATHY

Case No. and Name	Duration of Therapy	Approximate Total Steroid Dose (gm.)
ı, M. O.	20 mo.	Cortisone, 75 Prednisone, 1
п, J. R. M.	3 wk.	Cortisone, 3.2
m, L. B.	2 mo.	Prednisone, 2
ıv, R. M.	1 yr.	Cortisone, 90
v, R. S.	3 mo.	Prednisone, 10
vi, G. F.	11 mo.	Prednisone, 10
vn, E. G.	3 wk.	Prednisone, 0.8

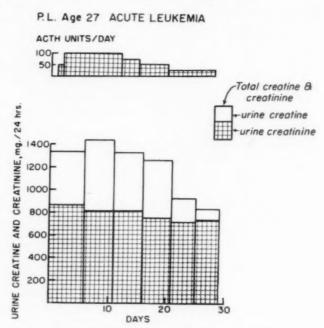


Fig. 4. Urine creatine and creatinine in a patient (P. L.) with acute leukemia treated with adrenocorticotrophic hormone.

signs of hyperadrenocorticism were evident and its character was such as to remind one of the muscular weakness encountered in spontaneous Cushing's syndrome.

The time between initiation of therapy and the patient's first awareness of weakness ranged from three weeks in two patients to twenty months in another. (Table III.) The muscle weakness was insidious in onset. The most frequent symptom was difficulty in climbing stairs. Next, rising from a squatting position became a major task. With continued therapy the weakness increased and, within two to four weeks, rising from a chair became difficult and walking without assistance was impossible. Four of the seven patients eventually became bedridden because of their muscular weakness. The deep pelvic and thigh muscles were most strikingly affected, but in three patients (M. O., R. S. and G. F.) weakness in the upper extremities also was present. Only one (L. B.) complained of muscle pain; one other (E. G.) had muscle cramps. Gross atrophy of muscle was usually present, particularly in the thigh and pelvic musculature. No abnormal neurological findings were noted in any of the patients.

Although the relationship between dose of steroid used and the development of muscle weakness varied, muscular weakness was, in general, most marked when large doses of adrenocortical hormones were administered over long periods. Symptoms appeared in two pa-

tients after relatively small amounts of prednisone had been given; others had taken from 2 to 10 gm. of prednisone or up to 90 gm. of cortisone before muscle weakness became apparent. (Table III.) About ten days after the steroid was reduced in dose or discontinued the patients noted return of muscle strength. Two to three weeks after cessation of therapy muscle strength had returned almost to pretreatment levels.

Pathological changes in the muscle were minimal. A distinct increase in sarcolemmal nuclei was noted in some fibers but this was not a constant finding. The most consistent feature was the presence, in scattered muscle fibers, of large, clear, empty vacuoles similar to those seen in the muscle of patients with familial periodic paralysis [6]. In addition to familial periodic paralysis, vacuolar degeneration has been described following heat damage to skeletal muscle, in gangrene, in degeneration following section of peripheral nerves, and in thyrotoxic myopathy [7]. Multiplication of sarcolemmal nuclei is found when muscle fibers regenerate after injury and may imply regenerative activity in the affected muscles in our patients. However, nuclear multiplication has also been observed in degenerative muscle disease unaccompanied by any other signs of regeneration [8].

Necrosis of skeletal muscle which cannot be modified by supplementary therapy with potassium chloride, thiamine or alpha tocopherol has been described in animals given ACTH or cortisone [10-14]. After five days of treatment with cortisone, 10 mg. per kg. body weight, the skeletal muscle of rabbits showed homogeneous, glassy muscle fibers which sometimes contained vacuoles of various sizes. The latter stained red with oil red O [13]. The histologic changes found in our muscle biopsies are similar to these; unfortunately, fat stains were not made in our patients. The advanced degenerative changes found in some of the cortisone-treated rabbits were not found in our patients. In the rabbit, regeneration of skeletal muscle occurred and all lesions healed when cortisone was discontinued [13]. The involvement of skeletal muscle rather than of other types of muscle, as well as the reversibility of the lesion in cortisone-treated rabbits, is similar to our experience in man. It is of interest that the creatinuria seen in our patients, like the muscle weakness, often was prominent at a time when their primary disorder was in remission. The creatinuria of patients receiving cortisone [16-18] as well as that of Cushing's syndrome has been ascribed to decreased tubular reabsorption of creatine [19]. It is unlikely that this was the mechanism of the creatinuria in our patients since the elevated serum creatine levels in our patients could not be explained by a decrease in the renal absorption of creatine.

The data in the patients with muscular dystrophy and with inflammatory disease of muscle treated with ACTH were somewhat variable, perhaps owing to the different doses and lengths of time of therapy. In spite of this, however, they may help to clarify the mechanism of creatinuria in patients in whom muscle weakness develops while receiving steroid therapy. In the dystrophic patients increased creatinuria usually developed while receiving ACTH, without demonstrable deterioration in muscle strength. This suggests that, at least for short periods, ACTH or steroid therapy may increase creatine synthesis. In the dystrophic subject, with impaired ability to store creatine in the muscle, this results in augmented creatinuria. In patients with inflammatory or other disease directly or indirectly affecting muscle, the improvement in the underlying disorder results in increase in muscle mass and improved ability to store creatine, with the result that, in spite of increased creatine synthesis, creatinuria decreases.

The lesions in animals treated with cortisone and the muscle atrophy found in our patients suggest the presence of an additional mechanism for creatinuria in our patients. Long-continued therapy with ACTH or steroids may damage human muscle in a fashion similar to that seen in rabbits. It is quite likely that, in this instance, creatine storage is impaired. This, combined with increased creatine synthesis, could account for the truly massive elevations of serum and urinary creatine in patients with the myopathy of steroid therapy.

It is difficult to determine the frequency with which muscle weakness occurs as a manifestation of exogenous hypercorticism. The patients reported here represent approximately 3 per cent of the patients with leukemia or hemolytic anemia seen in this clinic in the past five years. It is almost certain, however, that milder degrees of muscle weakness go unrecognized in patients whose complaints do not call attention to this sign.

Our studies do not clarify the pathogenesis of steriod myopathy of man or of animals. A factor which must be considered is loss of body potassium, since potassium deprivation will produce weakness as well as necrotic lesions of skeletal 898

muscle [9]. However, all of our patients received potassium supplements during steroid treatment. In addition, the oral administration of potassium does not alter the development of lesions

in cortisone-treated animals [13].

It has been suggested that the muscular changes encountered in hyperadrenocorticism result from an interference with protein metabolism [15] and that muscular weakness, together with osteoporosis and purple striae, is a clinical manifestation of protein deficiency in Cushing's syndrome. That 17-hydroxycorticosteroids influence protein metabolism is well known, but the explanation of the net catabolic effect is far from clear. It is possible that steroid myopathy results in part from deranged protein synthesis or destruction, but the observations reported in this paper neither confirm nor deny this hypothesis.

SUMMARY

1. Severe muscular weakness, which occurred during adrenocortical hormone therapy in seven patients, is reported.

2. After variable but relatively prolonged periods of administration of 17-hydroxycorticosteroids in comparatively large doses, deep pelvic and lower extremity muscle weakness and muscle atrophy occurred. After therapy was discontinued, muscle strength returned to normal.

3. Minimal histologic changes, consisting of scattered areas of muscle vacuolization and proliferation of sarcolemmal nuclei, were found

in biopsy specimens of the muscle.

4. Increased serum creatine levels and creatinuria accompanied the muscle disorder.

5. The effects on creatine excretion of ACTH and 17-hydroxycorticosteroid therapy in patients with progressive muscular dystrophy and inflammatory muscle disease suggest that increased creatine synthesis together with decreased ability to store creatine may be responsible for the creatinuria observed in the patients with steroid myopathy.

6. Steroid myopathy may be the limiting factor in the quantity of 17-hydroxycorticosteroids which can be tolerated by certain patients.

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"Psychogenic" Pain and the Pain-Prone Patient*

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In the past fifteen years, at two university medical centers, I have studied a large number of patients with pain. The great majority of these patients were seen in my role as a medical attending physician on the medical wards, teaching students and house officers, and as such included the usual variety of diagnosed and undiagnosed painful disorders ordinarily encountered on a medical service. A few patients were referred to me by colleagues who knew of my interest in pain. In addition, I have had random opportunities to observe the appearance and disappearance of pain during the course of psychoanalysis of patients with neuroses and psychosomatic disorders. The veiws about pain presented in this paper have evolved out of this clinical experience.

THE THEORETICAL PROBLEM

Pain is a cardinal manifestation of illness, and the relief of pain is probably the most common demand made by the patient upon the physician. In spite of this importance of pain, it is astonishing how little we understand pain, but how confident we are of our knowledge of pain. Perhaps familiarity breeds contempt. Every physician has his own personal experience with pain and it began long before he ever became a physician. This is in contrast to other complaints which we learn about only while studying medicine. The medical student, when asked what pain is, feels at once that pain is something familiar, although he may have great difficulty defining it in scientific terms. What he means is that he himself has experienced pain and hence "knows" what pain is. When he is taught that there are pain receptors, pain fibers, pain pathways, and a center for pain perception, his concept of pain becomes scientific. To the com-

fortable familiarity that comes from personal experience are now added these simple "facts" and from this a relatively simple concept of pain is constructed. Pain is the sensation which arises when pain receptors are stimulated and it is transmitted via its own fibers and pathways to the thalamus where it is perceived or experienced. The more thoughtful student usually notes that whatever is transmitted from the periphery must also somehow or other be perceived in consciousness, otherwise it is not pain. He may also note that people seem to respond differently to whatever it is that they perceive as pain. This insight then leads to the familiar formulation that pain has two components—the original sensation, and the reaction to the sensation. There the matter usually rests. When a patient complains of pain, it is taken for granted that pain end organs somewhere in the body are being stimulated, presumably by a pathological process. That this often proves to be the case provides repeated and comforting support to those who hold this centripetal point of view. When no such explanation is found, it is assumed that a pathological process is there nonetheless but simply has not yet been discovered. Rarely this too proves to be so. Or it is postulated that something is affecting the nerves ("neuralgia"), or the nerve pathways, or even the thalamus, producing so-called "central" pain. If no other explanation is forthcoming, the patient is told in one way or another that his pain is "imaginary," often meaning that the physician does not believe it exists, in spite of the most tangible evidence that the patient is suffering just as intensely as the person who has a visible and palpable painful lesion. In more recent years the term "psychogenic" pain has come into use and is generally applied by exclusion to those

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instances in which no other cause of pain can be demonstrated. For many this is a vague and mysterious concept since the commonly accepted concept of pain provides no room for such a notion. How can there be pain if pain end organs

are not being stimulated?

I emphasize these points because unless you can relinquish the notion that pain must originate in peripheral receptors and nowhere else, it is virtually impossible to understand what is referred to as "psychogenic" pain. Perhaps we need to ask first: What is pain? A definition of pain is elusive at best, if possible at all. As observers we cannot even recognize pain. Indeed, pain can only be experienced and for our information about pain we are totally dependent upon the report of the person experiencing it. As Szasz has pointed out, pain falls into the category of private data-experience which cannot be simultaneously shared and reported by anyone other than the person experiencing it [1]. It can only be reported. This is different from some varieties of experience, such as vision or hearing where what impinges on the sense organs can also be experienced by other observers and hence some consensus can be achieved as to what was seen or heard. Hence we have had no difficulty in discovering that occasionally persons may report seeing or hearing things in the absence of recognizable visual or auditory stimulation. One thinks at once of the hallucinations of psychotic people. However we should not overlook the fact that visual and auditory experiences in the absence of the corresponding peripheral stimulation are part of our daily life. Our dreams, for example, are predominantly and at times brilliantly visual in character—perhaps less often auditory. Some persons have a capacity for vivid visual and auditory imagery during the waking state. During complete sensory deprivation, including pitch darkness, there may be brilliant visual hallucinations [2]. A variety of chemicals, e.g., mescaline and lysergic acid, characteristically produce visual images [3]. Penfield has reported on the auditory experiences in temporal lobe epilepsy and during direct brain stimulation [4]. I make these points to emphasize that when it is possible to verify the presence or absence of a peripheral source of stimulation in studying sensory experiences, we have no difficulty in identifying a host of examples in which no peripheral stimulation takes place and yet the person clearly experiences

sensation. Arguing by analogy alone, I contend that the same must also hold true for pain.

What significance, then, are we to attach to the undoubted fact that there are pain pathways and that pain can be evoked by stimulation of parts of the body that are so innervated? Certainly it makes clear that in whatever manner we may conceptualize pain, one way in which it can be evoked is by appropriate stimulation of this peripheral sensory system. This does not justify the additional, usually inferred postulate that pain can result only from the stimulation of such pathways. But it does permit us to study and to identify characteristics of pain which are dependent on the neurophysiological characteristics of the peripheral system, an important consideration since this enables us to identify a pain process originating in muscle as compared to skin, for example. The peripheral distribution of pain-sensitive receptors has another importance in terms of how the individual's concept of pain develops. Pain belongs to the systems concerned with protecting the body from injury. We may assume that from birth on the individual builds up a library, so to speak, of pain experiences, originating from the variety of peripheral painful stimulations which he experiences during the course of his life. As we will show later, these are importantly concerned with the person's over-all development. Thus, from the developmental side we presume that the capacity to experience pain in the first place develops from numerous peripherally induced experiences but thereafter pain experience, like visual or auditory experience, may occur without the corresponding stimulation of the end organ.

There are still other reasons that compel us to question the purely centripetal concept of pain. We have already noted that only the sufferer knows whether or not he has pain and we may then ask: How does he know? Obviously consciousness and attention are necessary. Actually, the most successful technics for relieving pain, namely, general anesthesia and hypnosis, are not directed to pain per se but to consciousness and/or to attention. We know that the grievously wounded soldier in the heat of battle may experience no pain until the action is over.

Now, how do we know "pain" when it reaches our attention? We know it only by its quality and from this point on language fails us. It is completely impossible to describe pain accurately. We can describe it only in terms of experiences which evoke pain. Thus we may

describe it as "sharp," thinking of a cut or a quick blow; or "dull," thinking of some slow pressure; as "burning," "tearing," or like a "pin-prick" or "toothache," and so forth. Obviously these are not descriptions of pain—these are descriptions of circumstances under which pain actually was experienced, or our imagination of how it would feel were something of this sort to be experienced. The man with a coronary occlusion may say it *feels like* his chest is being crushed, even though he may never have experienced actual compression of the chest and were he to experience it he would discover that it did not resemble his pain of coronary occlusion at all.

When we scrutinize more carefully the identifying quality of pain we note that it includes an affective tone. Pain is never neutral. It is usually unpleasant, but it may also be pleasant, if only in a relative sense. This effective quality brings pain into a very central position in terms of psychic development and function. Thus pain acquires special meanings for the individual as follows:

(1) Pain warns of damage to or loss of parts of the body, and is part of the system for protection of the body from injury. It is, therefore, intimately concerned with learning about the environment and its dangers on the one hand, and about the body and its limitations on the other. We presume that what causes pain and the part that hurts are permanently registered in the central nervous system. We may, therefore, speak of "pain memories" and of a "body pain image," the latter referring to parts of the body which have been sites of pain in the past.

(2) In terms of development, pain is very much involved in human relationships (object relations). From infancy, pain leads to crying and to a response from the mother or some other close person. The association of pain → crying → comforting by a loved person → relief of pain, is an important determinant of tender love relations and helps to explain the "sweet pleasure" of pain. It is not the pain that is pleasurable, but the anticipation of reunion with a love object

* One is not able to re-experience a pain at will, but one may have memories about the pain. This is true of affects in general. Hence, the term "pain memories" refers to the ideational complexes, conscious and unconscious, associated with past pain experiences, stimulation of which may later give rise to pain. This pain is not the "old" pain anymore than the joy evoked by certain memories is the same joy that was felt on the occasion of the original joyous experience.

and the relief of the pain that are enjoyed. Certain individuals function as if the pain is worth the price.

(3) Fairly early in childhood, pain and punishment become linked. Indeed, in many languages the two words spring from the same root. This establishes another kind of communication between the child and adults, namely, pain is inflicted when one is "bad." Pain thus not only may come to signal that one really is "bad," and thereby become a signal for guilt, but also pain may become an important medium for expiation of guilt. Some children as well as adults welcome pain if it means expiation and forgiveness and, hence, reunion with the loved one. If pain serves to relieve guilt, pleasure in a relative sense is again involved.

(4) Pain also early becomes closely associated with aggression and power. The child quickly discovers the effects of inflicting pain on others and on himself. We will learn how by suffering pain one may control one's own aggression. The pleasure of the aggression is retained, but one's self is taken as the target.

(5) Closely related to the preceding is the connection between pain and real, threatened or fantasied loss of loved persons. Especially when there is also guilt for aggressive feelings toward such persons, pain may provide a psychic means of expiation. Further, as Szasz points out, the patient succeeds in reducing the feeling of loss by experiencing a pain in his own body which he then substitutes for the lost person [1]. He suffers more from the pain than the loss, so to speak. Later we will see how the patient's ideas of pain actually or presumably experienced by the lost person will determine the location of the patient's pain. The psychic logic of this is revealed in our language when we speak of a "painful loss."

(6) Pain may also be associated with sexual feelings. We know that at the height of sexual excitement pain may not only be mutually inflicted but actually enjoyed. When this becomes the dominant feature of the sexual activity, we recognize it as a perversion, sado-masochism. We will also discover some persons who prefer to experience pain rather than have sexual experience, the latter existing only at the level of unconscious fantasy.

When we examine the full gamut of circumstances, from the simple peripheral stimulus to the complex psychological components, we

must acknowledge that pain in final analysis is a psychic phenomenon. The two-component concept of pain, which speaks of the pain sensation and the reaction to pain, is misleading because it implies that pain can originate only from a "pain" receptor. Gooddy goes so far as to say: "There can be no pathways nor nerve endings for pain. The notion of pathways for pain is but a figment of the observer's mind." [5]. Instead he suggests that disordered patterns (rate, amplitude, time and space) in nerves or neural centers provide the neurophysiological conditions which may be experienced as pain, but they do not by themselves account for pain. Certain characteristics of the impulse patterns may influence the quality of pain, but they will not in themselves determine that it be pain. This certainly is consistent with the clinical observation that one can identify qualities associated with colic, for example, as differentiated from a toothache, qualities which arise from the properties of the particular anatomical system giving rise to the disordered impulse patterns. Thus such patterns originating in the periphery contribute certain qualities to the pain and determine where the patient locates the pain, but the total pain experienced is always a psychic phenomenon.

This brings us then to "psychogenic" pain. While the pain experience is only and always psychic phenomenon, it is nonetheless of both practical and theoretical importance to know whether or not what is being experienced as pain includes disordered patterns originating in nerve endings, just as we need to know whether or not a visual experience originated from light waves striking the retina. But the fact of a peripheral process does not necessarily mean pain, for we know that pathological changes may be associated with the most excruciating pain in one person and with little or no pain in another. By hypnosis, or with placebos, we may eliminate or induce pain without modifying to the slightest the nature of the pathological lesion [6,7]. The practical clinical problem really has to do with how the individual experiences pain. Clinical observation reveals that there are people who seem to experience pain with unusual intensity and frequency. With peripheral lesions they seem to suffer more pain than most people do, but often they suffer pain without any peripheral process. Among such patients the presence or absence of a peripheral disorder is not well correlated with the presence or absence of pain. Indeed we often find that the

discovery of the lesion and its removal or cure does not alleviate the pain, which may persist or even recur at a later date. In other words, there are certain individuals, whom we shall call "pain-prone," among whom psychic factors play the primary role in the genesis of pain, in the absence as well as in the presence of peripheral lesions.

Clinical psychologic studies of many painprone persons have by now provided us with a fairly good understanding of the determinants of this susceptibility to suffer pain [1,8-13]. The key comes through understanding how pain may yield pleasure. It is pleasure in a relative sense, that is, in place of something even more distressing. Beginning from a primitive protective system, pain evolves into a complex psychic mechanism, part of the system whereby man maintains himself in his environment. Both as a warning system and as a mechanism of defense, pain helps to avoid or ward off even more unpleasant feeling states or experiences and may even offer the means whereby certain gratifications can be achieved, albeit at a price. If we can understand this adaptive role of pain in the psychic economy, we can begin to comprehend how it is that certain persons actually seek pain, even to the extent of creating it as a purely psychic experience if no peripheral stimulus is available to evoke it.

THE CLINICAL PROBLEM

Let us now examine pain in terms of the problem as it is actually encountered by the physician, namely, a patient seeks medical aid because he is suffering from pain. I propose that we approach each patient with the following questions in mind.

(1) Are there pathological processes affecting nerve endings and leading to disordered patterns in nerve pathways which are being experienced as pain? (2) If such processes are present, can the character of the pain experience reported by the patient be fully, partially, or not at all accounted for by the distinctive characteristics of the peripheral pathological process? (3) How are psychological processes operating to determine the ultimate character of the pain experience for the patient and the manner of its communication to the physician?

All three questions are pertinent with every patient, although circumstances as well as patients differ in respect to how much attention each

question requires before our problem is solved. They acknowledge the principle that a peripheral factor may or may not be operating and that when it is operating it may not fully account for the pain experience. Further, they permit us to explore in more practical clinical terms the precise criteria which should enable us to make accurate interpretations. For example, if a man complains of epigastric pain, neither a normal gastrointestinal x-ray series nor one showing some irritability of the duodenal cap will, by itself, provide the explanation for the pain. The patient may or may not have a duodenal ulcer, and if he has a duodenal ulcer this may or may not account for the pain which he experiences. When we examine what is called the typical "ulcer pain" we realize that there are distinctive characteristics of the pain associated with duodenal ulcer which we can recognize as the qualities conferred upon the total pain experience by the type of the disordered impulses arising in the nerve endings in the region of the ulcer. It is these qualities which permit us to identify duodenal ulcer as compared to biliary colic. Our first concern, then, must be with how the patient describes his pain.

The Description of the Pain. The peripheral signature: The relatively good concordance among individuals as to the kinds of pain associated with particular pathological processes gives us our first clue as to what differentiates the peripheral contribution to pain experience from the rest of the pain experience. Gooddy spoke of "disordered patterns," referring to rate, amplitude, time and space, and we immediately recognize that what enables us to identify a particular pain experience as being associated with myocardial ischemia, or renal colic, or a perirectal abscess, or a bone metastasis, concerns how the specific anatomic and physiologic characteristics of the diseased part gives rise to these disordered "patterns" [5]. Wolff's meticulous study and demonstration of the varieties of pain evoked by stimulation of various parts of the head provides an excellent demonstration of the consistency of the signature conferred on the pain experience by anatomical and physiological factors [14]. With a stone in the ureter, we can predict with a high degree of confidence where the patient will locate the pain and we will recognize in the colicky character of the pain the rhythmic contractions of the ureter in its attempt to pass the stone. Further, once we understand the anatomy and physiology of the structure in-

volved we can also predict that certain movements, postures and behaviors of the patient are chosen because they are associated with pain amelioration, while others are avoided because they are associated with the intensification of the pain. * While this is common knowledge, I stress it because the precise elucidation of such correlations between anatomical and physiological characteristics on the one hand, and pain experience on the other hand, provides the most certain evidence that processes originating in the periphery are initiating a particular pain experience. Conversely, deviation from these understandable anatomical and physiological principles should immediately caution the physician that peripheral disordered patterns either play no role or their influence is being obscured by other factors. The patient, for example, with acute myocardial infarction who continues to experience the same pain unremittingly for a week arouses our suspicion. Does this indicate a further extension of the infarct? This is an unlikely possibility and would have to be established by means other than the pain itself. Could it be that pain that originated in relationship to the myocardial infarct now has established an existence independent of the changes taking place in the myocardium? Finally, could it be that the pain never was related to the myocardial infarct, but rather to something else which again may or may not be affecting nerve endings? The incongruity between the pain characteristics as described by the patient and the known pathophysiological and pathoanatomical processes is in itself sufficient grounds to question the accuracy of the interpretation which explains all on the presence of the allegedly demonstrated peripheral disorder. Here I would warn especially against the commonplace practice of describing such situations simply in terms of the pain being "atypical."

The individual psychic signature: As we listen to the patient's account of his pain, we first attempt to detect and identify pain qualities associated with stimuli arising from the periphery, as just described. All the other features of the pain description are understandable in terms of what we might call the individual's "psychic signature," as contrasted to the "peripheral signature." What are some of the varieties of

^{*} In the two person field we may also note that certain movements, postures and behaviors are utilized by the patient with pain because of their value in communicating to others the need for help.

pain description that are not understandable in terms of a peripheral process, even when the latter is present? I have already mentioned discrepancies in respect to what would be predicted from anatomy and physiology. We need to pay attention to pain location in terms of the patient's concept of his body image as contrasted to pain location determined by the distribution of nerves. For example, the patient who locates his pain in the region of the left nipple or the apex beat may at some point indicate concern about heart disease. The doctor should consider the possibility that some idea about heart disease accounts for the location of the pain, although not for the pain itself, rather than the pain giving rise to the idea of heart disease. Actually, patients with heart pain often prefer to explain the pain on the basis of something non-cardiac, such as indigestion.

Patients' private concepts of how their bodies function may influence their description of pain. For example, the person who entertains an autointoxication theory may get pain relief from cathartics or colonic irrigations, such relief not indicating in any way colonic disease. The intensity of pain reported by patients is a highly individual matter. Clinical experience is a useful guide but, in general, gross deviations in either direction inform us more of the psychic state of the individual than of the existence or nature of a peripheral lesion. Libman's test for pain sensitivity by styloid pressure is a useful way of evaluating quickly how a patient deals with a painful peripheral stimulation [15].

In general, the more complex the ideation and the imagery involved in the pain description, the more complex are the psychic processes involved in the final pain experience. In part this is a matter of reality testing. When the pain experience is initiated from the periphery and this is the primary factor responsible for its presence, and when the function of the pain is to signal to the patient damage or injury to a part of his body and nothing else, the pain description is likely to be economical and relatively uncomplicated. Terms such as "sharp," "dull," "aching," "throbbing," and the like are relatively easily applied and the relationship to physiological processes relatively easily identified by the patient. On the other hand, vague descriptions as well as more elaborate imagery are reflections of the degree to which the pain is entering in psychic function in a more complicated fashion, now serving purposes far beyond the simple nociceptive function. While the patient almost

always initially presents his complaint as a pain, an ache, a headache, a backache or some such symptom, request for elaboration will sometimes, but not necessarily, bring out a vague description, as "a sensation," "an unpleasant feeling," "I just can't describe it"; or descriptions such as "being jabbed with an icepick," "burning like a red-hot coal," "bruised and torn," "like my face is being eaten up," "electric shocks burning me," and "just too horrible to describe." Or "headache" may become "a sort of pressure as if the top of my head would come off." A backache may become "a pulling or drawing as if the cords of my back were being pulled at." Sensations described as boring, gnawing, biting, penetrating, crawling, twisting and tearing are particularly meaningful. Now these varieties of description are extremely valuable in identifying the presence or absence of a peripheral process. In general, however, while we can be fairly confident of a peripheral lesion when the description is not only crisp and economical but also concordant with anatomical and physiological processes, we cannot conclude that the patient who gives us the more complex, the vague, or the vivid type of description does not have a peripheral lesion. Such descriptions reflect the characteristics of the individual and if he is suffering from a peripheral lesion, the disordered patterns arising from it are subjected to the most complex psychic distortion and elaboration so that at times the peripheral qualities may be totally obscured.

This now brings us to explore who are the patients disposed to use pain in this fashion and under what circumstances do they do so. For convenience we shall refer to them as the "pain-

prone patients."

The Pain-Prone Patients. For the most part these patients repeatedly or chronically suffer from one or another painful disability, sometimes with and sometimes without any recognizable peripheral change. There are also patients who may have only a single or occasional episode of pain, among whom essentially the same psychic mechanisms are operative. Such patients by no means constitute a homogeneous group and yet they have many features in common. By recognizing and understanding the clinical expressions of the psychodynamic processes underlying this type of psychic function of pain, the physician will be able to recognize the patient who uses pain in this fashion and hence more correctly interpret each pain experience for which he is consulted.

The choice of pain as symptom: pain as punishment: I mention this component first because clinical observation leads me to conclude that guilt, conscious or unconscious, is an invariable factor in the choice of pain as the symptom, as compared to other types of body sensations. Clinically we should expect to find either a long-term background of guilt and/or an immediate guilt-provoking situation precipitating pain. The clinical characteristics of the chronically guiltridden person are not difficult to recognize, if one appreciates the role of penitence, atonement, self-denial and self-depreciation as means of self-inflicted punishment to ease the feeling of guilt. The patient who uses pain as a means of self-punishment and atonement almost always manifests other psychological and behavioral devices which serve the same purpose, and their recognition will alert the physician to the likelihood that this patient is indeed using pain in this fashion.

Some of these individuals are chronically depressive, pessimistic and gloomy people whose guilty, self-depreciating attitudes are readily apparent from the moment they walk into your office. They seem to have had no joy or enthusiasm for life and, indeed, some seem to have suffered the most extraordinary number and variety of defeats, humiliations and unpleasant experiences. You may first be inclined to pass this off as a consequence of the pain they are suffering or as just a matter of bad luck. But it quickly becomes apparent that many of these difficult situations have either been solicited by the patient or simply not avoided. They drift into situations or submit to relationships in which they are hurt, beaten, defeated, humiliated and, to our astonishment, seem not to learn from experience; for no sooner out of one bad spot they are in another in spite of the most obvious danger signals. At the same time they conspicuously fail to exploit situations which should lead to successes and, indeed, when success is thrust upon them they do badly. This provides the clearest proof that these characteristics are not the result of the pain, for we note often that it is just when life is treating them worst, when circumstances are the hardest that their physical health is likely to be at its best and they are free of pain. Paradoxically, when things improve, when success is imminent, then a painful symptom may develop. Unconsciously they do not believe that they deserve success or happiness, and feel that they must pay a price for it. A common kind of statement is, "When I was

having such a hard time, I felt good; but now, just when I should be able finally to enjoy myself, this terrible pain has to come." Even though they complain of the pain, for them the pain is almost a comfort or an old friend. It is an adjustment, a way of adaptation acquired through psychic experience. We are often struck by the disparity between the intensity of the pain and suffering they describe and their general appearance of well-being. Some patients may describe a terrible pain with so little evidence of current suffering that you may be surprised to discover that they are speaking of a present pain. This stoical behavior may express the need to see oneself and be seen as a martyr who tolerates suffering. Other patients display intense suffering, behavior which also has psychic determinants, including a need to appear as the suffering person, to be pitied, or to be succored. Some patients seem to experience a secret joy in their pain while others appear literally to be persecuted by it. Many of these patients are unusually tolerant of pain inflicted upon them by nature or by the physician in the course of examination and treatment. In their histories we discover an extraordinary number of injuries and operations and more than the usual number of painful illnesses and pains, the latter usually described in medical jargon as "pleurisy," "kidney attacks," "sinus," "lumbago," "appendicitis," and the like. Careful history will usually render doubtful that such terms actually correspond with the diagnosis in more than a few instances. We soon realize that what many of the patients solicit from us is the infliction of further pain, usually in the form of surgery or painful diagnostic or therapeutic measures. Treatment that is not painful or a hardship may be rejected. Physicians may be surprised at how well these patients tolerate painful procedures. Indeed, the patient who is very fearful of such painful procedures is not likely to be found among this group at all.

The following cases are illustrative:

A sixty-one year old man had suffered intense pain intermittently for twenty-five years in the region of the right ear. This pain had lasted for several days at a time and was described as "raw and burning." The patient's mother had died when he was seven and a half years old. His father and stepmother had treated him harshly, and "boxing the ears" was a frequent punishment from both, a procedure to which he had submitted passively, although his younger brother had not. Characteristic of this man was that he had allowed himself to be struck by his father until his

twenty-first birthday, feeling that he had no right to protest until he was legally an adult. However, he did not leave home until he was twenty-six years old and up to that time had contributed the major share of his earnings to his father. Face pain began about this time.

Although of superior intelligence, he had done heavy manual labor for many years. Later he had gone into business with a partner. The business was a success, but his partner had soon cheated him of all the profits and he had ended up losing everything. Like other events in his life, he had accepted this without a struggle.

Six years before examination, he had suffered a myocardial infarction and since then had experienced severe angina pectoris decubitus. The face pain be-

came less severe from that time on.

A fifty-three year old unmarried school teacher had had severe dysmenorrhea and headaches since the age of eighteen. At various times in her life she had had severe pains in her head, cheeks, teeth, abdomen, back, legs and hips. The low back pain had been described as "like a raging toothache—sometimes like something is moving or crawling down my legs." She described a fantastic career of suffering, of which the

following sequence is typical:

She had worked hard for almost thirty years, depriving herself of all comforts in order to build herself a house in which to retire. In the meantime she lived with an old woman who suffered from senile dementia and who made excessive demands. Finally the long-awaited day arrived and she moved into her new home. She soon began to feel guilty enjoying this all by herself, so she advertised for a roomer. She took in a young couple with two small children who soon spread out to occupy the whole house, the patient retiring to a single bedroom. When the new tenants complained that she interfered with their privacy, she had obligingly moved out, sold them the furniture at a loss, rented them the house for a ridiculously small sum and had returned to live with the senile lady.

With many of these patients we will be struck by the dramatic fashion in which they describe both the hardships of their lives and the extent of their suffering from pain, illness, and the slings and arrows of misfortune. Indeed, this very dramatic quality and the relish with which they recount the story, often an almost unbelievable one, should immediately alert the physician that this is a person for whom pain and suffering are unconscious sources of gratification.

A forty-four year old woman had a host of painful symptoms beginning in adolescence. At various times they included "appendicitis," "arthritis," "pleurisy," "kidney colic," "heart" pain, face pain, back pain, headaches and pains in the extremities. She had had fourteen major and minor operations and at least five painful injuries. Everything in her life was described in dramatic terms. The patient's relation to her mother had been a very ambivalent one, while towards her father she had felt most affectionate as a child. She had especially enjoyed resting her face on his shoulder. She recalled an occasion when she was twelve years old when her mother had had severe pain in the face due to a tooth infection. Although she was extremely frightened of the dark, she ran a considerable distance at night to get a doctor.

Early in childhood she felt her mother favored her four siblings. She deliberately provoked her mother by misbehaving and when her father came home from work she expected to be punished and indeed often was. This was actually a pleasurable experience because, after the spanking, her father would hold her on his lap and fondle her. She had many fears in childhood and would find these an excuse to jump into her father's bed for comfort. When she first began to menstruate she thought she was bleeding to death. When she was twenty-two years old she married a boy she hardly knew and her life with him was a nightmare. They lived with his mother who treated her as a servant. He drank, beat her, and openly brought prostitutes to the house and required his wife to wait on them. Occasionally she would leave her husband for a few months at a time but she always returned. At these times she lived with her well-to-do physician brother and his wife where she functioned essentially as a servant. When her father and later her mother became ill, she undertook the complete responsibility of their care.

Her father died in her arms when she was thirty. Following his death the mother became depressed, and this depression lasted several years. The patient undertook her care and never left her alone. The first and only time the patient went out, her mother took the opportunity to commit suicide by throwing herself in front of a train. The body was badly mutilated and no one was permitted to see it. The patient repeatedly attempted to reassure herself that her mother's face had escaped mutilation. After her mother's death she finally brought herself to divorce her husband. At the age of forty she married a sixtyyear old man. Commenting on this marriage, the patient stated that she would be content to settle for ten years of happiness. She called her husband "Daddy." No sooner had she entered what she called the first happy period in her life, when she quarreled with her sister-in-law and physician brother. Then the face pain developed which already had robbed her of the first four of her hoped-for ten years of happiness.

The development and backgrounds of the painvulnerable patients: For practical clinical purposes it is usually not necessary to elucidate all the

factors predisposing to these developments. Suffice it to say that we often find that aggression, suffering and pain played an important role in early family relationships. These may include: (1) Parents, one or both of whom were physically or verbally abusive to each other and/or to the child. (2) One brutal parent and one submissive parent, the former sometimes an alcoholic father. (3) A parent who punished frequently but then suffered remorse and overcompensated with a rare display of affection, so that the child became accustomed to the sequence, pain and suffering gain love. (4) A parent who was cold and distant but who responded more when the child was ill or suffering pain, even to the point that the child invited injury to elicit a response from the parent. (5) The child who had a parent or other close figure who suffered illness or pain for which he came to feel in some way responsible and guilty, most commonly because of aggressive impulses, acts or fantasies. (6) The child who was aggressive or hurting until some event suddenly forced an abandonment of such behavior, usually with much guilt. (7) The child who deflected the aggression of a parent away from the other parent or a sibling onto himself, usually an early manifestation of guilt. Some of these backgrounds are illustrated in the following excerpts of the histories of pain-prone patients. It is consistent with their psychological characteristics that these patients readily provide the physician with such information if only he indicates his interest to hear it. This eagerness to tell of such distressing life experiences is in itself of diagnostic value, and it is not of crucial importance whether such descriptions are factual or fanciful. In either event, the fact and manner of telling betrays the wish of the patient to present himself as long-suffering and abused.

A thirty-two year old married woman had cruel, impulsive parents. The father was a chronic alcoholic and the mother unpredictable and sadistic. She had vivid memories of being hit hard across the face and back by both parents. Mother would slap her face suddenly and without warning as insurance against future misdeeds. When the patient was seven, all of mother's teeth were extracted; the patient remembers the severe face pain suffered by the mother.

A thirty-four year old married woman witnessed the death, by accidental burning, of her two year old sister when she was five. This little girl's clothes caught fire from a wood stove and her face was badly

burned. Later the parents separated and she was placed with an older couple. The foster mother frequently beat her about the face and head and pulled her hair. The patient said, "I often think of her when I have my pains."

A twenty-seven year old married mother had pain in the head, face and eyes. As a child she frequently witnessed her brutal, alcoholic father slap her mother across the face. Her sister, seven years younger, was born blind in one eye. The patient blamed the father for this and also accused him of preventing the girl from receiving proper medical attention. She herself undertook to obtain this care for her sister at the expense of great personal hardship.

A forty-one year old unmarried woman, a school teacher, had severe sharp pain involving the entire left half of the face and head. Since childhood she had always maintained the strictest control over the expression of any aggression. As a child, however, she had had a reputation of being a little "spitfire." This period came to a close when, in a fit of anger, she threw a pair of scissors which stuck in the left cheek of her little cousin. The mother warned her that retaliation in kind would befall little girls who throw things and put people's eyes out. From that time on she never actively expressed aggression externally.

Alternating with the face pain had been back pain. When she was sixteen her father was killed in a mine accident. That day he had awakened with a backache and although his wife urged him to stay home and rest, he went to work and as a consequence was killed.

Under what circumstances does the pain occur?: Many of these people have had repeated episodes of pain, so that this question has two aspects: when did the patient first have pain and when did each episode occur? Quite a number have their first significant painful syndromes in adolescence. This is especially so among women patients whose story may begin with painful menarche, dysmenorrhea, or headaches, especially premenstrual. A very important clinical finding is the history of "appendicitis" and appendectomy. These episodes do not fit the usual clinical picture of acute appendicitis, but usually involve chronic or intermittent abdominal pain of quite varied nature and severity, sometimes associated with a variety of other symptoms. Such attacks usually begin in the age range fourteen to eighteen years, eventually leading to appendectomy. When surgical records are available we find the appendix reported as "normal" or "chronic appendicitis." Curiously, this pain usually disappears after

surgery, although it may soon be replaced by other pains often related by the patient and some physicians to the scar or to adhesions. This "appendix" syndrome is much more common among girls than boys and its presence in the past history provides a valuable clue for the

interpretation of later pains [16].

The onset of pain syndromes in adolescence also reflects the important psychological changes occurring in this period of life and especially the sexual conflicts that may be involved in the genesis of pain. Both guilt about sexual impulses and an unconscious sado-masochistic concept of sex are important. Pain may occur in lieu of or may prevent sexual activity, and hence under circumstances in which sexual impulses might be aroused, in fact or in fantasy. Frigidity, dyspareunia and varieties of impotence are common accompaniments. Or the patient may enjoy some sexual pleasure if he is hurt (masochism). Along these same lines we may discover painful, mutilating and destructive concepts of pregnancy and labor, among men as well as among women.

We may now consider some of the circumstances under which individual episodes of pain may occur, remembering that this may also include pain precipitated by unconsciously motivated accidents or injuries. While our discussion so far has focussed on the patients with the most pronounced pain vulnerability, we should keep in mind that there are also persons among whom the specific psychodynamic constellation conducive to pain may be activated on

only a few occasions in their lives.

(1) When external circumstances fail to satisfy the unconscious need to suffer: We have already commented on the patient in whom pain develops when things begin to go well. These are always individuals with an exaggerated need to suffer who may remain relatively pain-free as long as external circumstances make life difficult. When the environment does not treat them harshly enough or they cannot get it to do so, it seems almost as if they inflict pain upon themselves.

A forty-five year old woman had at various times abdominal pain ("chronic appendicitis"), back pain, and finally severe pain in the left side of the jaw, left ear and left side of the temple. She described the latter as "like a jab with an icepick." Although she came from a wealthy and socially prominent family, at the age of twenty-five she married a ne'er-do-well who cruelly mistreated her. She was humiliated by the divorce three years later. She remarried twelve

years later and although this was a good marriage it was marred by a series of distressing deaths, injuries and illnesses in her family. In spite of the fact that small children irritated her, she adopted two little boys in rapid succession when she was over forty years old. She was always getting sick. Her face pain began just at a time when things finally seemed to be going well for the first time, and after she had consented to allow her paralyzed mother-in-law, whose care she had undertaken at great personal sacrifice for many years, to go to a nursing home.

A thirty-two year old woman married to a brutal, alcoholic man who frequently beat her and the children, and who provided for her most inadequately, struggled hard to maintain herself. She began to suffer a series of painful disabilities when her husband underwent a religious conversion, gave up drinking, and became the model of a conscientious and considerate husband and father. Just when she had everything to live for, her pain prevented her from enjoying it.

Such precipitating circumstances are easily overlooked if the physician fails to recognize that for certain persons, success and good fortune are stressful in that they mobilize intolerable feelings of guilt [17,18]. These persons really feel that they do not deserve happiness or success and they must suffer to achieve it.

(2) As a response to a real, threatened, or fantasied loss: Following the death or any permanent loss of a loved person, or during the period of anticipation of such a loss, the survivor may develop pain during the period of mourning and sometimes on anniversaries of the mourning. Szasz has pointed out how the mourner may take a part of his own body as a love object in place of the lost person and by experiencing pain in this part, symbolically assure himself of its continued presence [1]. He designates pain as an affect that warns of the danger or threat of loss of a body part. I agree with this formulation but find it incomplete, for it does not sufficiently include the affect of guilt. While following the loss of a loved person one becomes more selfcentered and sometimes more aware of body sensations (or also at times less aware), this is not experienced as pain by the sufferer unless there is also a strong element of guilt, most often related to ambivalence toward the lost person. In a study of patients with ulcerative colitis we observed that if a relationship with a love object was threatened by some overt or unconscious aggressive act or fantasy and the patient responded with guilt, then pain (usually headache) developed; if the patient responded

with feelings of despair, helplessness or hopelessness, activation of the colitis was the more usual response [19].

A classic illustration of pain in response to a sudden loss is illustrated in the following case:

A forty-two year old woman had a brief attack of sharp pain in the left anterior chest. In the interview she almost immediately began to speak of how upset she had been since the shotgun murder of her brotherin-law one week earlier. He was shot in the left side of the chest. His body was taken South for burial, but she had to remain home to care for the children. She cried when thinking or speaking of this event. She greatly admired and was very fond of this man who was a stable and successful man in the community. In contrast, her husband (the victim's brother) was irresponsible and abusive. In fact, exactly one year earlier, while drinking, he brutally beat her and then threatened to shoot her with a shotgun. She averted this by clutching her infant to her chest and jumping out the (ground floor) window. She preferred charges against him and he was currently on probation. Further interview strongly indicated a guilty wish that the victim had been the husband rather than

While many episodes of pain occur in direct relationship to the loss of a loved person, as in this case, many more occur in relation to threatened losses, anniversaries of losses, or fantasied losses. Thus we may find pain developing in relationship to the illness or impending departure of important family members or friends, where the patient responds with, or had previously experienced aggressive feelings toward such persons. Or the patient may experience the loss or its anniversary as a painful reminder of guilt, and actually suffer with it in the form of pain.

(3) When guilt is evoked by intense aggressive or forbidden sexual feelings: There are some individuals for whom any expression of aggression is unacceptable and even the threat or possibility that aggression might be expressed provokes guilt. Some of these persons instead experience pain, sometimes without any aggression being expressed and sometimes remorsefully after it has been expressed. After the pain develops, the provoking situation may be forgotten or only vaguely remembered or the patient may recall it remorsefully, consciously accepting the pain as a punishment and as a warning against future expressions of aggression. Some patients observe that their pains occur when they do not control themselves.

A thirty-two year old woman, who also had had ulcerative colitis, was compulsively clean and always kept close rein on any expression of aggression. Her two and a half year old son defecated in his crib and smeared the feces. She became furious and immediately spanked him. A few hours later a severe headache developed. She felt remorseful for her outbreak of temper and resolved not to do so again. The headache was considered a deserved punishment.

When the provoking situation involves sexual impulses, these, in contrast to the aggressive impulses, are almost always at an unconscious level and must be inferred by the examiner. In general, they involve situations which might normally be expected to be sexually exciting, but are not so recognized by these patients, who instead experience pain; or more subtle situations in which the precipitating stimulus has special symbolic meaning to the individual, generally reminiscent of some childhood sexual conflict. Pains so experienced follow the classic model of the hysterical conversion mechanism, in which the pain simultaneously expresses symbolically the forbidden impulse and at the same time successfully prevents it being acted upon. When the conversion symptom is pain, we find that along with the sexual impulse there is always a strong aggressive component and guilt. The sexual fantasy is a sado-masochistic one.

A twenty-six year old woman with a variety of hysterical manifestations had several episodes of pain and burning at the end of urination. The urine examination was always negative but she referred to it as "my cystitis." One episode occurred during her first year of marriage. Her husband proved less capable sexually than she hoped for and she felt both frustrated and angry. As a child the bathroom was the scene of many sexual fantasies and of masturbation, which included poking things in and around the urethra. These symptoms recurred briefly during the course of psychoanalysis when her husband had a severe case of flu and was sexually inattentive for several weeks. She developed fleeting sexual fantasies about the analyst and then her "cystitis" recurred. The painful dysuria promptly disappeared when these transference sexual feelings were brought up during the analytic hour and connected with the childhood fantasies and masturbatory activities.

The location of the pain: The patient usually describes the pain as occurring in some part of his body, whether it originates there or not. When no peripheral factor is operating, the

patient still assigns a location to the pain. This choice of site of the pain is determined by one or more of the following:

(1) A peripherally provoked pain experienced by the patient sometime in the past: In essence, the patient revives unconsciously a past pain experience and by mechanisms not understood suffers again from pain of the same character and in the same location as the original pain. This may be the pain of a past injury, an operation, or any physical disorder which had occurred at a time when the pain could fulfill, directly or indirectly, a psychic regulating role for the patient. It may have been punishment or it may have been the vehicle whereby a relationship was re-established. Some postoperative and post-traumatic pain syndromes are of this sort.

A young man had repeated bouts of severe searing shocks of pain in the right side of his forehead. These came on with explosive suddenness, sometimes associated with a sensation of flashing light and staggering, and were followed by a dull, throbbing pain of

growing intensity.

When he was twelve years old he prepared a home-made bomb, one of numerous aggressive act unconsciously directed toward his stern and punitive father. The bomb exploded prematurely and he suffered a depressed skull fracture as well as the loss of several fingers of his left hand. He felt extremely guilty and considered the accident a deserved punishment. The location and character of the head pain exactly duplicated the original accident. The pain characteristically occurred in settings in which anger toward authority figures was blocked by guilt. Sometimes he could terminate the pain by an attack of blind destructive fury against some inanimate object, such as a piece of furniture.

The widest variety of painful disorders in the past may provide the basis for future pain experiences and a careful history often will uncover the original painful incident as well as the psychological factors operating at the time. When the current pain, which may be described in terms identical with the original pain, is not also accompanied by the appropriate physical or laboratory findings, especially when this occurs in a person with the other characteristics of the "pain-prone" population, the diagnosis is strongly suggested. This is illustrated by the patient with ear pain who in the past had otitis media; the patient with throat pain who once had a peritonsillar abscess; the patient with painful dysuria and frequency and normal urine who once had acute cystitis.

(2) A pain actually experienced by someone else or a pain the patient imagined or wished the other person experienced: This is perhaps the most common and the most important determinant of the site of the pain. It involves several important psychologic mechanisms. First of all, the other person is important to the patient and is one with whom the patient is in some (usually unconscious) conflict or from whom he has been or may be separated. Secondly, it involves the psychic mechanism of identification, meaning that the patient unconsciously becomes like the other person, notably in terms of suffering like him. We have already mentioned real, threatened or fantasied losses and guilt for forbidden impulses as precipitating factors. We can now add that the location of pain may be determined by the real or fantasied location of pain in the other person(s). It must be emphasized that this is unconscious. The patient is unaware of a connection between his pain and the pain of the other person and if directly questioned will never consciously make the connection, although he may unconsciously reveal it by word or gesture. On the other hand, if the physician meticulously explores the history of pain and illness of all the important persons in the patient's life he will usually uncover without much difficulty the model for the patient's pain. To do this the patient is asked to describe the symptoms of each person, paying particular attention to the patient's idea of the pain.

A forty-two year old man complained of severe stabbing pain in the region of the left nipple. This occurred while he was out hunting and just taking aim at a buck deer. He felt fearful, had difficulty breathing, became lightheaded and collapsed. The patient's father had died of a "heart attack" the previous fall. The medical student who took the history assumed that the patient knew his father's pain had been substernal. When asked where his father's pain was the patient said, "I don't know," but he pointed to the region of his own pain.

Sometimes we know the other person's illness to be painless, only to discover the patient thought otherwise. Thus edema of the ankles may be assumed to be painful, or dyspnea may be thought to be an expression of pain. In such cases the patient may describe the pain he believed the other person to have suffered in the same terms he used to describe his own pain. There is little chance of overlooking such relations if one always gets the patient's description.

One may even ask, "What did you imagine it was like?" The cases already noted have provided a number of examples of this mechanism. The following cases offer additional data.

A forty-one year old unmarried woman, a teacher, lived with and took care of her ailing mother for many years until her death one month before the beginning of the patient, s face pain. She slept in the same bed as her mother. On the night of her mother's death she had awakened to find that the right side of her mother's face was drawn and a short time later it became blue. She was breathing heavily and the patient believed her to be suffering great pain. She called for help but when unable to secure any climbed back into bed only to realize that her mother was dead.

She had been engaged to a man for many years but had not married because she could not leave her mother. However, upon her mother's death, she first felt emancipated, and bought a house, but then pain developed in the right side of her face and because of it she gave up both her home and fiancé. She expressed remorse at her feelings of emancipation after her mother's death and consciously considered the pain as punishment, a sign that she was being inconsiderate of her mother's memory.

A forty-seven year old married woman had experienced strong guilt when her only daughter was born twenty-two years ago with a cleft palate and harelip. She felt that this was the result of her husband's practice of coitus interruptus. When her doctor implied that this might have resulted from clumsy attempts at abortion, she said, "That was just like a slap in the face to me." The patient's mother also had indicated by innuendo that she believed her daughter was in some way responsible for the baby's defect. The mother suffered from erysipelas of the face fifteen years ago and the patient took care of her. The mother has had face pain from time to time since then. The patient's face pain began one month after the daughter underwent the first of a long series of plastic operations on her face. The patient commented, "I am doing the suffering for her." The patient imagined that her daughter suffered great pain from these procedures, although actually this was not so.

In this last case we note how the choice of location may be overdetermined, here involving not only the daughter's facial deformity and operations, but also the "slap in the face" and mother's erysipelas and face pain.

A thirty-one year old married woman had severe pain in the right side of the neck and throat, radiating into the shoulder, right eye and cheek. This had developed while she was taking care of her mother who had suddenly acquired erysipelas of the face. It began while the patient was undergoing treatment from the chiropractor who was taking care of her mother and who had recommended a chiropractic treatment as a prophylactic measure. When asked what part of her mother's face was involved by the erysipelas, the patient was unable to recall, but placed her hand over the painful area of her own face.

Among other symptoms, a twenty-three year old married woman had severe throbbing pain in the temporal regions radiating into the eyes. Her soldier husband had been injured in combat. He had sent her a photograph of himself in which he had cut out the left eye with scissors, indicating that this was the extent of his injury. The patient's symptoms began a week later. It developed that just before he went overseas she had learned that he had been involved in an extramarital affair. She was so angry that she struck him violently in the eye, knocking him down. Under pentothal hypnosis she told how much she wanted him punished. "I wanted him to get as much hurt as I was. I hoped he would get his leg or his foot, or his privates shot off." While he was overseas she had a brief affair, over which she felt very guilty. It was shortly after her lover had left her that she received the news of the husband's injury and the photograph. She was tremendously concerned at his possible retaliation for her infidelity and her pain began when she received word that he was being shipped home.

Sometimes the site of the pain is determined by a conscious or unconscious wish that the other person suffer pain. This may have appeared only as a fleeting thought or may not have been associated with the person at all. This is illustrative of the intrapsychic operation of lex talionis, the patient inflicting on himself exactly what he wished on the other person.

We can understand these determinants of pain location in terms of the importance of object relations (interpersonal relations) in the maintenance of health and of psychic balance. They are expressions par excellence of attempts to maintain object relations, albeit at a price. It is as if the patient says, "If I can't continue to have this relationship and get from it what I want and need, I will become like him in some way." This is a generally used mechanism to deal with a real or threatened loss, but in these cases, mainly because of guilt and the role of pain in past relationships, the patient experiences the object's pain, real or fantasied. By such a psychic experience of pain the patient simul-

taneously denies the intensity of the loss and atones for his guilt.

Psychiatric diagnosis: While similar psychodynamic features may operate, these patients do not constitute a homogeneous group in terms

of psychiatric nosology.

(1) Conversion hysteria: The largest number of these patients satisfy the requirements for the diagnosis of conversion hysteria and their histories usually reveal many other conversion symptoms, such as globus, fainting, aphonia, sensory or motor disturbances. They manifest the relative indifference to or exaggerated display of symptoms, as well as the dramatic, exhibitionistic, seductive or shy behavior so common among hysteric persons. They are suggestible and may have intense emotional involvements with the physician, often associated with dramatic remissions and relapses of symptoms. To varying degrees they may have been involved in acting out behavior, including drinking, use of drugs, and sexual promiscuity. The men patients are often relatively passive and have feminine identification, usually with the mother. A peculiarly intense interest and preoccupation with hunting, especially solitary hunting has, in my experience, been a common finding among the men. The hysterical patients with pain generally differ from those without pain in the prominence of sadistic and masochistic elements in their sexual developments, usually with pronounced guilt.

The following case is a classic example of conversion hysteria with pain as a prominent manifestation. It is presented in detail because patients with conversion hysteria constitute the largest percentage of the pain-prone population and a thorough study of this case protocol will be richly rewarding in illustrating the characteristic features of hysterical patients with pain. Interpretative comments, in brackets, call attention to some of the characteristic features of psychogenic pain and the pain-prone patient discussed in the body of this paper.

A twenty-seven year old married woman, a singer by profession, had suffered from pain in her face and head for many years. She was first seen in February 1945. She felt she could distinguish at least three kinds of pain. At about the age of eleven or twelve she began to have attacks of pain in the right side of the face. This pain became extremely severe during a pregnancy which ended in a spontaneous abortion at three months in October 1944. The attacks usually began as a dull ache over the right eye, and rapidly progressed to a severe throbbing pain involving the entire right side of the head and face, and radiating into the neck and shoulder. This was associated with tearing of the right eye, stuffiness of the right nostril, and at times flushing and hyperesthesia of the right side of the face. The pain was made worse by movement and noise, and when severe was associated with nausea and vomiting. Such attacks lasted a day or more.

A second type of face pain consisted of sudden brief shooting pain of moderate intensity involving the right cheek and followed by a dull aching pain. This pain had been present intermittently for about a year.

The third pain was of several years' duration and consisted of a sudden sharp, burning pain arising at .he angle of the right jaw, radiating into the teeth, along the ramus, and into the ear. This pain generally came on when she was about to eat. It was associated with increased salivation. Generally it lasted several minutes and then subsided, permitting the patient to go on with her meal. She was examined for salivary duct calculus but none was found. Detailed examination, including neurologic, roentgen and dental study, revealed no abnormalities.

At first the patient stated that her general health was and always had been good and that if it were not for the face pain she would be entirely well. It soon became evident that this was not so. She also suffered from attacks of nausea and vomiting; she was "sensitive" to many food items which induced nausea, vomiting and urticaria a few minutes after ingestion and sometimes simply on sight; she had attacks of bloating and swelling of the abdomen; she had shaking chills, with chattering of the teeth; and a subjective feeling of great coldness, during which her hands and feet would blanch and become icy cold; she had attacks of breathlessness, dizziness, and numbness and tingling, during which she occasionally lost consciousness; paroxysms of cough occurred which could not be explained on the basis of any respiratory tract disease, although she had had two to three attacks of rather typical bronchial asthma in her life; she had dyspareunia and was totally frigid; she suffered with urinary frequency and urgency. [Other hysterical conversion symptoms.]

The patient, an only child, was born in Chicago in 1918. Both parents were exceedingly neurotic persons. The mother was a successful business woman at the time of her marriage, although it was rumored that her success was partially accounted for by being the mistress of her employer. Unable to get him to marry her, she impulsively married her present husband as a spiteful gesture. He at this time was a rather inconsequential but handsome man, who so far had been quite unsuccessful in establishing himself as a business man. His wife paid his debts, set him up in business, and thereafter never permitted him to forget her role. For a period he was quite successful, but in 1928 he

lost all his money and went heavily in debt. Since then he has held only small jobs and tends to use alcohol to a considerable degree. [Aggressive, controlling mother; relatively passive father.]

The patient felt the parents' marriage to be entirely devoid of any love or affection. They quarrelled frequently and violently. The patient always felt in the middle. She recalled one occasion when her mother threw a hammer at her father, and another occasion when he hit her mother with an ash tray. Not infrequently she had witnessed them strike each other in the face during quarrels. [Prominence of aggression in early family relations.] During such scenes the little girl felt she had to separate the two combatants "lest the quarrel end in murder." She consciously directed the parents' anger toward herself in order to avoid their hurting each other. On one occasion she scratched her father's face to "bring him to his senses." [As child, deflects aggression to herself.]

The patient said the mother avoided any sexual contact with father and besides she believed he was impotent anyway. "Mother could scare anyone into impotency." She was not born until the parents had been married nine years, when they were thirty-five years old. The mother carried on a constant harangue against her father. She repeatedly warned the patient to have nothing to do with men and especially to avoid sexual contact. Even after the patient's marriage mother continued to urge her to have a separate bedroom as she herself had. [Mother's hostility to men and fear of sex.]

In 1938 the father was discovered to have cancer of the urinary bladder. The mother openly taunted him with the diagnosis and expressed pleasure that she would now be free of him. [Mother's sadism.] A subtotal cystectomy was performed and the father recovered, although he was left with frequency of urination. More recently the father had had a heart condition and was short of breath. [Factors in patient's "choice" of respiratory and urinary symptoms.]

During the early contacts with the patient she was most bitter toward her mother, whom she described as argumentative, domineering, nasty and hypercritical, with no love for her. After such attacks on the mother, however, the patient would have the impulse to call her on the phone, and then would feel remorseful because her mother seemed more kind and interested than she had described her to be. [Hostility to mother, guilt, and submission.] On the other hand, she first described her father as "sweet and nice." He had beautiful curly hair and he would let his little daughter play hairdresser and fuss with his hair for hours. Later on, statements changed and she said he was "wishy-washy, inconsistent, and an opportunist," that he "always disappointed me." "My dream castle is nothing but a backwoods shed," was her comment after a visit from father. [Disappointment with father.]

As a little girl she had tried to get close to her father, but her mother would never permit this. Mother would either make fun of any show of affection between the two or would fly into a rage and accuse them of conspiring against her. On many occasions the mother threatened to leave home and when father and daughter begged her to stay, she ridiculed them. Several times the mother spent all day in a movie to simulate such a threat. [Mother's sadism.] The little girl was heartbroken. Father always dealt with mother's threats by giving in. He wanted peace at any price.

The patient described herself as a difficult child to take care of. She devised various technics to provoke or exasperate her mother. One was to hide her mother's prized possessions, tell her she had hidden them but not where. This generally led to a spanking. [Patient's use of pain and punishment as way of relating to mother.]

At a very early age she demonstrated unusual ability in singing. The mother had a "magnificant voice" and cultivated her little daughter's talent, functioning for a period as her teacher. When she was nine she won a singing contest and made her debut with a nationally known symphony orchestra. Following the concert her mother pointed out that Mozart had made his debut at an earlier age. [Mother's depreciating and rivalrous attitudes.] Thereafter the patient concentrated on her singing, studied with well known teachers, and made several public appearances. She progressed rapidly in school, finishing high school at fifteen, and college at twenty. For a while in college she lost interest in a career as a singer; but after graduation she joined a light opera company which toured the country. She often had the leading soprano role and received good press notices. Her mother, however, always depreciated her performances.

Her early sexual education was very strict. Her mother depreciated all things sexual, and warned the child against any sexual activity. She kept her from wearing attractive or feminine clothing, opposed her fixing her hair, and insisted that she wear glasses although she had no need for them. In high school and college she was known as "Prudence Prim." Her mother would not permit her to go out alone until she was twenty-one years old, saying only bad girls went out. She was not permitted to live away from home. In early adolescence she fought hard to get away and mother let her go to boarding school. After a few months mother brought her home because she thought she was having too good a time. [Mother's depreciation of femininity and sexuality. The patient submits.] Her menses began at eleven, two weeks after an auto accident (which will be described in detail later). Although she had been told about menses, she thought they were the result of the accident.

The patient was married in August 1942. She had not previously gone out with many men, although she

enjoyed their company on an intellectual basis. She liked to be with a group of men on a "man to man basis." She had had no sexual experience until marriage. [Patient's masculine identification and sexual inhibitions.] She had gone with her husband about two months when they became engaged; they were married six months later. He was in the army at that time and stationed near Boston awaiting embarkation. Immediately after the ceremony coughing and wheezing developed which became so severe over the course of the next two weeks that she felt compelled to go home to Chicago. [Asthma in response to first real separation from mother.] As she stepped from the train and was met by her mother her asthma ceased and did not recur. The next day her husband was shipped overseas and she felt guilty that she was not there to see him off.

The patient worked in a war plant during her husband's absence and held a rather responsible position. She lived with her parents. In the fall of 1943 her husband returned to the United States to convalesce from an attack of pleurisy and she joined him. In June 1944 she became pregnant and felt disgusted in spite of the fact that she had been trying to get pregnant for several months and was beginning to worry about sterility. During the pregnancy she had a great deal of nausea and vomiting and almost continuous severe head and face pain. She remained very active and "heaved furniture around." [Patient's self-destructive behavior.] Three months later she aborted while visiting her mother. She first felt very panicky and then became somewhat depressed. [Guilt.] She had the thought that she had not long to live and that her husband would be unhappy if she died. She behaved provocatively toward him and deliberately irritated him. " . . . so that he would hate me and would not miss me and could remarry." Several times she made the gesture of packing her bags and leaving. At other times she provoked the neighbors, sometimes by her singing, and she often got herself into unhappy situations with tradespeople and friends. [She provokes attacks on herself.]

During the period of therapy there occurred a number of experiences during sleep which her husband wrote down and brought in for discussion. The patient had complete amnesia for these experiences but was able to bring important associations. Two such episodes were particularly revealing.

(1) One night she said while asleep, "He hit me in the face with a buckle. I was a naughty girl." This recalled an incident at age four. She had been naughty and mother insisted that father punish her. He was undressing. As he pulled his belt from his pants he suddenly struck her violently in the face with the buckle end. [Determinants of the face as location of pain.] "I remember hating him violently after that." Once, at eighteen, during a violent quarrel between the parents, the patient thought, "If he hits me, I would murder him." Just before her husband was

discharged from the army she impulsively threw all his belts into an incinerator. They made her feel very uncomfortable, but as she watched them burn she had a happy feeling of triumph. This reminded her that mother had often used father's belt to strike her. [Unconscious association between father and husband. Aggression and guilt.]

Later she brought up that on two occasions she had provoked her husband to the extent that he had slapped her face. A severe exacerbation of face pain

resulted on both occasions.

(2) The most dramatic episode concerned the auto accident to which she had briefly alluded in the first interview. At the time she merely said that she had been in an auto accident at age eleven, and that she suffered a fractured kneecap and was in a cast for a year. She did not mention any injury suffered by mother. [First face pain began when the patient was eleven or twelve.]

While asleep the patient tossed restlessly and began talking. [Reliving a traumatic episode.] "I know he didn't have any lights on. He turned them on after he got to the middle of the street. We never start to cross the street without looking." She cried out in pain, "My knee, my knee! That morphine makes me see the lights all over again. That car is rolling mother down the street and it isn't going to stop. I can't stand that car rolling her. I see her face full of blood. The eye is cut. She is dead. My face, my face, my face hurts." [Injury to mother's face as determinant of site of pain.] The patient beat on the bed. She awakened and appeared terrified. "I have to get up and see if I can walk." She struggled with her husband to get up, but was unable to. Her teeth chattered violently and she had a shaking chill at this point. "I am cold like I was sitting in the snow that night." The husband observed: "She was breathing rapidly and her arms and legs were icy cold. There was decided swelling of the right cheek which was red and hot over the area of pain. I sensed this temperature change by contrasting the two sides of the face. She writhed, clutched, and gasped, so intense was the pain. A cold object pressed against the pain area produced a shocking feeling in the face. "Light hurt her eyes." In referring to the shortness of breath the patient commented, "It feels as if someone is sitting on my chest." [Origin of other conversion symptoms.]

The patient was then able to describe the accident in more detail. It occurred in a suburban district at night where it was quite deserted. It was a cold wintry night, 13°F. below zero with snow on the ground. Mother and daughter stepped from the street-car and started to cross the street. Suddenly they realized a car without lights was bearing down on them. Just before striking, the headlights were turned on and glared in their eyes. Mother raised her hand to protect her face. She was struck by the car and dragged a half a block. The patient was knocked to her knees and found herself alone in the dark sitting in

the snow. She screamed; she felt alone and deserted. She shivered with the cold and it seemed endless before anyone picked her up. When she saw her mother, her face looked "like someone had beaten it with a hammer." Mother was coughing up blood. The patient was brought to a hospital where she received morphine and had repetitive frightening dreams of the accident. Her mother, who recovered quickly, brought violets, which remain the patient's favorite flower. The patient remained in a cast for a year and was taken care of at home by her mother. She described this as a not unhappy time. "I was completely helpless. Whenever I have been ill, mother has been good to me." [Love from mother when she suffered.]

(2) Depression: Another group of patients suffers predominantly from depression. The generally depressed appearance, the retarded or agitated behavior, the content of speech, the expressed affects of sadness, guilt and shame, all identify the depression and this is usually documented by history. Some patients, it will be found, have had previous episodes of depression without pain and some are the chronically gloomy and depressive characters already described. A common error by the physician is to assume that the patient is depressed because he has pain. Investigation will usually make clear that the experience of pain serves to attenuate the guilt and shame of the depression. Indeed, in some instances the pain is clearly protecting the patient from more intense depression and even suicide. This group of patients in particular may become addicted to drugs.

(3) Hypochondriasis: The hypochondriacal patient experiences and communicates his pain or other body sensations in a distinctive way. One quickly notes its peculiarly intense and persistent quality. It may not be as severe as it is inescapable, annoying and bedeviling, and the patient is made desperate by the pain. As the physician listens to the patient's description he immediately notes the urgency with which the patient seeks relief and his tremendous concern as to what the pain means. He often seems more concerned with the interpretation of the pain, is it cancer or some terrible infection, than with the pain per se, and he is little or not at all reassured by the doctor's examinations. There is often a distinct quality of being persecuted by the pain. At the same time it will be found that the patient lavishes all varieties of attention and care on the painful part, somewhat in contrast to the relative indifference of the hysteric patient or the long-suffering attitude of the depressive patient. Some of these patients are prepsychotic.

(4) Schizophrenia: Closely related to the hypochondriacal patients are those who are psychotic and whose pain represents a delusion. Many of these patients are not recognized as psychotic simply because their complaint is pain. But the alert physician will note the following qualities. The patient truly feels persecuted by his pain and he seeks help with a desperation that is impressive. It is not so much that it is painful as that it is unrelenting, annoying and inescapable. The description of the pain may include bizarre ideas which are expressed as vivid analogies or as actualities. A pregnant woman had pain in the lower part of her abdomen. She ascribed this to being poked by the erect penis of her unborn child who she knew was a boy. Little further inquiry was needed to establish the diagnosis of schizophrenia. Patients express convictions that certain extraordinary changes have taken place in their bodies, the very bizarreness of which makes their delusional quality evident. A fiftyfive year old man with repeated attacks of abdominal pain said with conviction that his intestines were "twisted like a mop" and had to be untwisted, and begged for surgery. He also was convinced that there was some strange object in his abdomen, perhaps left in during previous surgery. Such patients usually manifest other paranoid qualities, including suspicious accusations against other physicians as being responsible for the pain. Or they may ascribe the pain to various outside influences, including rays and vibrations. A very important clinical point is the patient's tendency to associate the pain with nasal or rectal difficulties. Indeed these patients often first approach otolaryngologists or proctologists, or they may have sought treatment with colonic or nasal irrigations. The diagnosis will rarely be overlooked if the patient is given sufficient opportunity to present his explanation for the pain. This usually proves to be a complicated delusional concept.

It is perhaps important to mention here that often the schizophrenic patient either experiences no pain or does not complain of it when an ordinary painful disorder develops. An acute coronary occlusion or a perforated appendix may be entirely silent as far as the observer is concerned. Actually, pain is experienced in a delusional fashion by the schizophrenic relatively infrequently.

SUMMARY

* The general principles formulated in this paper may be summarized as follows:

1. What is experienced and reported as pain is a psychological phenomenon. Pain does not come into being without the operation of the psychic mechanisms which give rise to its indentifiable qualities and which permit its perception. In neurophysiological terms this also means there is no pain without the participa-

tion of higher nervous centers.

2. Developmentally, however, pain evolves from patterns of impulses arising from peripheral receptors which are part of the basic biologic nocioceptive system for the protection of the organism from injury. The psychic experience, pain, develops phylogenetically and ontogenetically from what was originally only a reflex organization. This may be compared to the necessity for functioning eyes and ears to receive light and sound waves before the complex psychic experiences of seeing and hearing can evolve.

3. Once the psychic organization necessary for pain has evolved, the experience, pain, no longer requires peripheral stimulation to be provoked, just as visual and auditory sensations (hallucinations) may occur without sense organ input. When such are projected outside the mind (in contrast to a painful thought or a painful frame of mind) they are felt as being in some part of the body and are to the patient indistinguishable from pain arising in the periphery.

- 4. Since the experience, pain, and the sensory experiences from which it evolves are part of the biologic equipment whereby the individual learns about the environment and about his body, and since this has a special function as a warning or indicator of damage to body parts, pain plays an important role in the total psychologic development of the individual. Indeed, pain, along with other affects, comes to occupy a key position in the regulation of the total psychic economy. We discover that in the course of the child's development, pain and relief of pain enter into the formation of interpersonal (object) relations and into the concepts of good and bad, reward and punishment, success and failure. Pain becomes par excellence a means of assuaging guilt and thereby influences object relationships.
- 5. From the clinical viewpoint we discover that disordered neural patterns originating in

the periphery confer certain qualities on the pain experience that permit the physician to recognize their presence and hence make a presumptive diagnosis of an organic lesion.

6. Clinical psychological studies of all varieties of patients with pain reveal that some individuals are more prone than others to use pain as a psychic regulator, whether the pain includes a peripheral source of stimulation or not. These pain-prone individuals usually show some or all of the following features:

(1) A prominance of conscious and unconscious guilt, with pain serving as a relatively

satisfactory means of atonement.

(2) A background that tends to predispose to the use of pain for such purposes.

(3) A history of suffering and defeat and intolerance of success (masochistic character structure). A propensity to solicit pain, as evidenced by the large number of painful injuries, operations and treatments.

(4) A strong aggressive drive which is not fulfilled, pain being experienced instead.

- (5) Development of pain as a replacement for a loss at times when a relationship is threatened or lost.
- (6) A tendency toward a sado-masochistic type of sexual development, with some episodes of pain occurring in settings of conflict over sexual impulses.
- (7) A location of pain determined by unconscious identification with a love object, the pain being either one suffered by the patient himself when in some conflict with the object or a pain suffered by the object in fact or in the patient's fantasy.
- (8) Psychiatric diagnoses include conversion hysteria, depression, hypochondriasis and paranoid schizophrenia, or mixtures of these. Some patients with pain do not fit into any distinct nosologic category.

CONCLUSION

I would like to close with a historical note. It is astonishing how little discussions of pain in standard textbooks of medicine have changed in a hundred years. In a textbook published in 1858 Wood discusses pain in terms which differ only in details from what appears in Harrison's "Principles of Internal Medicine" published in 1954 [20,21]. These details mainly concern more recent knowledge about the anatomy and physiology of nerve pathways. In both sources it is taken for granted that pain arises from the

periphery or in the nerves themselves. The most modern explanation of chronic pain is that "recurring painful stimuli from the periphery set up reverberating circuits related to the central activating system which influence, and are in turn influenced by the cerebral cortex so that there may develop a syndrome or chronic pain" [22]. In all these writings, psychological processes are relegated to a purely subsidiary role, such as reinforcing the reverberating circuit, or are simply dismissed by saying that the neurotic (or, in 1858, the "nervous") patient is less tolerant of or has a lower threshold for pain, clearly a cultural prejudice for which there is no scientific evidence. It is all the more remarkable that this state of affairs should continue to exist when, as early as 1895, Breuer and Freud in "Studies on Hysteria" published detailed case histories demonstrating convincingly pain as a psychogenic manifestation [8]. In contrast to much of Freud's later writings, this early work includes a wealth of case material. The modern physician, regardless of his knowledge of or attitudes toward psychoanalysis, will find it richly rewarding to read these case histories, for in them he can learn for himself the nature of the data and observations which permitted Freud to discover how pain may develop as a purely psychic phenomenon. Freud himself was not primarily interested in pain, but it happened that among many of these patients pain was a common and prominent manifestation, as were a great number of other somatic symptoms which also proved to represent hysterical conversions. Indeed, one might be justified in saying that psychoanalysis came into being through the clarification of the mechanism of some of these mysterious pain syndromes.

This leads to an interesting question, namely, how is it that this contribution to the understanding of pain has had so little influence on medicine in general, even on psychoanalysis. I believe the explanation is to be found in the peculiarities of medical practice. Freud began his practice as a neurologist and, in Vienna in the 1880's, undiagnosed pains were considered to be forms of neuralgia, an affection of nerves, concerning which the neurologist was the expert. As long as Freud was known primarily as a neurologist and his technic was not recognized as a form of psychotherapy, many such patients were referred to him and most went willingly enough. As he evolved into a psychoanalyst and the technic of treatment became increasingly recognized as a

psychological one, there must have occurred a change in the categories of patients who were considered suitable for referral. Further, patients with conversion hysteria, who suffer primarily from somatic symptoms, are reluctant to seek psychological help. In general, they regard their symptoms as organic in origin, a belief in which they are often supported by their physicians. The pain patients in particular are among the most reluctant to accept a psychiatric referral and to participate in psychotherapy if they do so. As time went on, Freud's practice consisted more and more of patients with the classic neuroses and with few exceptions this trend away from patients with somatic symptoms, including conversion hysteria, has continued to date. It is of interest in this respect that in Freud's early works, pain is referred to frequently, but later on one rarely finds any mention of pain. In the current scene, the analyst or psychiatrist is rarely consulted directly by a patient because of pain and only infrequently are such patients referred, and when they are many do not accept the referral. Thus the analyst and psychiatrist have had little opportunity to study this problem, which remains as common and difficult as ever. A large percentage of patients who consult physicians of all types belong to the group of "pain-prone" patients and are seeking help for painful disorders such as I have described in this paper.

This brings me also to the technic of investigation of these patients. Again, let me refer back to the original case histories of Breuer and Freud. These patients were not psychoanalyzed in the sense that we now understand the term. Every physician is free to rediscover for himself what Freud discovered about pain if he follows two simple principles: permit the patients to talk freely and take seriously what the patient says. If, in addition, he has some understanding of the psychic function of pain as I have outlined it in this paper, he will have no difficulty in confirming the observations of Freud as well as of those who followed him. This is not the place to discuss in extenso the technic of medical interview. Suffice it to say that an interview technic which permits the patient to speak of himself, his family, and his relationships as well as of his symptoms, which does not force a separation between what is regarded as organic and what is regarded as psychological or social, will be tremendously productive in clarifying the patient's illness. We have learned now that when

one knows what one is looking for, this can be accomplished in a remarkably brief time. I have seen some patients in whom the basic dynamics of the pain, including an explanation of the choice of the pain and its location, could be worked out in as little time as thirty minutes: with a great number of patients an hour's interview will suffice. But even when more interview time than this is required, this is more economical in time and expense for both the physician and the patient than the currently traditional technic of "ruling out organic disease" and attempting to establish a diagnosis by exclusion. Such interminable diagnostic procedures may not only be a waste of time and money but may also render virtually impossible the establishment of correct diagnosis simply because the patient himself becomes increasingly oriented towards this type of approach and less spontaneous in revealing personal and psychological data which the physician, by his approach and behavior, has made him feel are completely out of place. Needless to say, the physician whose technic of interview does not permit the patient spontaneously to reveal personal and psychological data along with his symptoms will not succeed in confirming the observations reported in this paper. But neither, for that matter, will the physician who uses only Sabouraud's medium to examine urethral discharges succeed in confirming the relationship between the gonococcus and some cases of gonorrhea. As in all matters scientific, the application of the appropriate method is indispensable.

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Clinicopathologic Conference

Diarrhea, Abdominal Pain, Gastrointestinal Bleeding, Chylous Ascites and an Intra-abdominal Tumor

S TENOGRAPHIC reports, edited by Lillian Recant, M.D. and W. Stanley Hartroft, M.D. of weekly clinicopathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine, Preventive Medicine, and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

A SIXTY-NINE year old white retired merchant (H. V.), entered Barnes Hospital on October 10, 1958. He died on October 12, 1958. His presenting complaints were abdominal pain and rectal bleeding of sixteen hours' duration.

In 1956 the patient had noted the onset of recurrent episodes of diarrhea which were frequently associated with tension-producing situations. The stools contained mucus, but never blood. Such episodes were occasionally noted to occur an hour after eating and were often associated with dull, non-radiating lower abdominal discomfort, frequently relieved by the occurrence of a diarrheal stool. These bouts increased in frequency during the six-month period before this hospitalization. Neither nausea, vomiting, melena, blood in the stool nor bleeding tendencies had ever been noted. The patient had consulted several physicians, and after a complete medical work-up, including roentgenographic gastrointestinal examinations and proctoscopy revealed no abnormalities, it was believed that his symptoms were of a functional nature.

He was treated with antispasmodics and dietary restriction, with symptomatic improvement. The patient's most recent examination had been three months prior to his admission to Barnes Hospital.

The day before admission, the patient began to pass frequent, frankly bloody stools. He also noted the recurrence of dull non-radiating lower abdominal pain. Bloody diarrhea persisted with increasing frequency until the time of admission. On the day of admission the patient had an emesis consisting of mucoid non-bloody material.

Although the patient's average weight was 168 pounds, two years before admission his weight had been 150 pounds, and at the time of admission his weight was 157 pounds. There was no history of epigastric pain, food intolerance, flatulence, eructation or jaundice.

In 1938 the patient had had an episode of severe epistaxis following an upper respiratory infection which had necessitated a blood transfusion. Beginning two years prior to admission he had had occasional bouts of dizziness for which he received an unknown medication with apparent relief. There was no history of syncope, weakness or diaphoresis.

On physical examination the patient was a thin, pale, white man who was neither in acute nor chronic distress. He was resting comfortably, and appeared to be a reliable historian. The vital signs were: blood pressure 120/70 mm. Hg in the right arm, pulse 76 per minute, respirations 16 per minute, and temperature 37.1°c. The skin was pale but otherwise normal. There was no significant lymphadenopathy. The peripheral pulses were palpable but of poor quality. There was no edema nor articular deformity of the extremities. Examination of the eyes revealed conjunctival pallor, but was otherwise within normal limits. The remainder of the examination of the upper respiratory tract was within normal limits except for pallor of the mucous membranes. The neck was supple, the thyroid not palpable, and there was no cervical venous distention with the patient in the supine position. The thorax was symmetrical with equal respiratory excursions. No abnormalities were noted upon percussion and auscultation of the

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chest. Examination of the precordium revealed the cardiac point of maximal impulse to be 9 cm. to the left of the mid-sternal line in the fifth intercostal space. The rhythm was regular and the heart sounds were not unusual. One observer noted the presence of an apical systolic thrill, a grade 2 apical blowing systolic murmur transmitted into the left axilla and a diastolic sound at the same location along the grade 1 aortic systolic and diastolic murmurs. These murmurs were not heard by many others seeing the patient. The aortic second sound was of the same intensity as the pulmonic second sound. The abdomen was flat. There was moderate tenderness in the lower quadrants upon deep palpation without muscle guard or rebound. The hepatic edge was palpable at the right costal margin. There were no signs of ascites. No other organs or masses were noted, and bowel sounds were active. The external genitalia appeared normal; and rectal examination revealed only prostatic enlargement. The neurologic examination was within normal limits.

The laboratory data were as follows: Hemoglobin, 11.2 gm. per 100 ml.; white blood cells, 11,250 per cu. mm.; with monocytes, 3 per cent; lymphocytes, 21 per cent; segmented forms, 76 per cent; and band forms 10 per cent. On examination of the blood film adequate numbers of platelets were evident. The urinalysis revealed a specific gravity of 1.017; reaction, 6.5; determinations for protein and reducing substances were negative and examination of the urinary sediment disclosed no abnormalities. Stool examination revealed a strongly positive guaiac reaction. The reaction to the cardiolipin test for syphilis was negative. Blood type was group A, Rh positive. Blood chemistry determinations were as follows: sodium, 143 mEq. per L.; potassium, 3.7 mEq. per L.; non-protein nitrogen, 50 mg. per cent; fasting blood sugar, 197 mg. per cent; calcium, 9.6 mg. per cent; phosphorus, 3.1 mg. per cent; uric acid, 2.8 mg. per cent; alkaline phosphatase, 3.0 Bodansky units; and acid phosphatase, 0.3 units. Total serum proteins were 4.1 gm. per cent, with albumin 2.8 gm. and globulin 1.3 gm. per cent. The prothrombin time was 100 per cent of normal. The serum glutamic oxaloacetic and pyruvate transaminase determinations were within normal limits.

Shortly after admission the patient underwent proctoscopic examination which revealed fresh blood throughout the 22 cm. examined. No abnormalities of the colonic mucosa were noted.

Transfusions were instituted at the time of admission. Rectal bleeding continued and during the first twelve hours of hospitalization the patient began to complain of paraumbilical pain. Following this, an episode of hematemesis occurred. Surgical consultation was requested and laparotomy was advised.

At laparotomy, a large retroperitoneal mass was found involving the uncinate lobe of the pancreas and the root of the mesentery. The mass lay in front of the third portion of the duodenum, and completely surrounded the mesenteric artery and vein with fixation of the latter structures. There probably was invasion of the mesenteric vein because large dilated varices were noted over the serosal surface of the involved portion of the duodenum. Because of the extensive involvement of the mesenteric root structures and the duodenum, resection was not possible. Attempts to locate and establish operative arrest of the bleeding site were unsuccessful. Several biopsy specimens were taken from areas of the mass and were interpreted by the surgical pathologist as "probably malignant islet cell tumor" of the pancreas.

Postoperatively the patient's course was one of progressive deterioration. He continued to have large bloody stools and to display frank blood on nasogastric suction. Despite attempts to maintain blood volume the patient's blood pressure continued to fall and he died twenty-four hours postoperatively.

CLINICAL DISCUSSION

Dr. Sol Sherry: Today's discussion centers about a sixty-nine year old white man who, two years before his first and only admission to Barnes Hospital, noted the onset of recurrent episodes of diarrhea. The bouts of diarrhea were frequently associated with eating, and were preceded by lower abdominal discomfort. The patient had undergone repeated physical and roentgenographic examinations, but an organic basis for his attacks could not be established. Dr. Scheff, would you review the roentgenographic findings?

DR. HAROLD SCHEFF: These roentgenograms were taken in January 1956, about three years ago when we saw the patient for the first time. At that time he gave us a history which is a little bit at variance with that in the protocol.

He described recurrent diarrhea for about eight or ten years and also episodes of epigastric pain coming on about one or two hours after his meals. He also had some nocturnal distress. Roentgenograms of the gastrointestinal tract showed slight elevation of the greater curvature of the stomach but no defects in the stomach. There was some irritability of the duodenal cap. A roentgenogram taken four hours after the barium swallow showed complete emptying of the stomach. Throughout the entire small intestine the pattern of the mucosa was abnormal. There was some involvement of the terminal ileum which was suggestive of enteritis.

DR. SHERRY: These observations are quite different from that presented in the protocol and were not available in the chart. Dr. Scheff, I presume you believed there was an organic basis for the complaints. What was your diagnosis?

DR. Scheff: We treated this patient for a probable duodenal ulcer. Therapy included antacids and antispasmodics, and the patient obtained remarkable relief of his symptoms. His diarrhea improved at that time.

DR. SHERRY: Did he have hyperacidity?

Dr. Scheff: Gastric analysis was performed once and the patient had considerable amounts of free acid.

DR. SHERRY: Dr. Nickel, you observed this patient for a period before his hospitalization. Are there any additional comments you would like to make?

DR. JAMES NICKEL: When I saw the patient he had obtained complete relief from his epigastric distress. He had adhered to the ulcer regimen until he obtained relief; then he went off the diet, but had no recurrence of epigastric discomfort. He came to me complaining of frequent, loose stools. He had very vague lower abdominal discomfort, occurring more in the lower left quadrant than in the right, with an urge to defecate, and relief with defecation. He had noted no blood in his stools. He refused any extensive work-up, having been studied thoroughly in Dr. Scheff's office. Sigmoidoscopic examination was repeatedly within normal limits. Stool examination did not reveal any evidence of blood or excessive numbers of white cells, and the rectal and sigmoid mucosa were always within normal limits. He was treated with a low residue diet and antispasmodics. He gained weight and improved symptomatically. Until the final complaint of bleeding, he had

little or no difficulty in the two or three months prior to his death.

DR. SHERRY: Was there anything abnormal about the bowel movements or the stool other than the presence of diarrhea?

DR. NICKEL: No. There was never excessive fat in the stool, nor was it malodorous or frothy. The stool was simply loose and somewhat watery in consistency. There was nothing to suggest a malabsorption syndrome at any time.

DR. SHERRY: Sixteen hours before admission, the patient began passing frankly bloody stools and hospitalization was advised. Physical examination was within normal limits. Laboratory examination revealed a mild anemia and leukocytosis, a moderately elevated blood urea nitrogen presumably associated with the bleeding, an elevated fasting blood sugar, and some hypoproteinemia. The patient received multiple transfusions but rectal bleeding continued. The patient then noted some paraumbilical pain and an episode of hematemesis occurred. Dr. Hershey was consulted and he advised surgery. Dr. Hershey, what did you expect to find at surgery?

DR. FALLS HERSHEY: At the time I was asked to see the patient, he already had received 6 or 7 pints of blood, yet the bleeding was continuing. In addition, by this time he had vomited blood and it seemed quite certain that the source of the bleeding lay in the stomach or the duodenum. In view of the extent and persistence of the bleeding, operation was undertaken.

My preoperative diagnosis was a bleeding peptic ulcer. The postoperative diagnosis was hemorrhage due to invasion of the duodenum by a malignant tumor involving the root of the mesentery. The tumor was contiguous with the uncinate lobe of the pancreas and surrounded and invaded the portal vein and the superior mesenteric artery.

DR. SHERRY: In patients with massive bleeding in the upper gastrointestinal tract, how frequently is a bleeding peptic ulcer the cause?

DR. Hershey: Well, we have been fooled in several instances. Excluding the bleeding esophageal varices, there have been 180 such cases treated surgically at the Veterans Hospital and in seven an unusual cause has been found, such as lymphoma, tuberculosis of the duodenum, mesenteric thrombosis and acute gastritis. I would estimate that 90 to 95 per cent of massive bleeding in the upper gastrointestinal tract would be due to peptic ulcer, varices or gastritis.

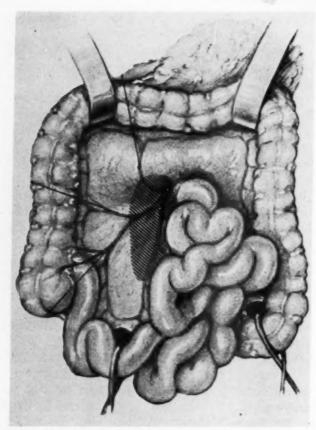


Fig. 1. Anatomical drawing showing the extent and location of the tumor mass found at surgical exploration.

DR. Scheff: I would raise that to 95 per cent. DR. Sherry: Therefore, the presence of bleeding due to some other cause than those just mentioned would be relatively unusual. Dr. Hershey, would you tell us what you actually found at operation?

Dr. Hershey: We opened the abdomen through an upper abdominal incision, and blood was seen in the duodenum at the ligament of Treitz. Blood was not visible in the first and second portion of the duodenum and the stomach and duodenum appeared entirely normal. We immediately came upon this large mass. Figure 1 is a drawing showing the extent and location of the tumor. This drawing is an anatomical exposure rather than the view through the surgical incision. The mass crossed the front of the duodenum and invaded the mesocolon so that it lay against and involved the uncinate lobe of the pancreas. The main extent of the mass, however, lay in the small bowel mesentery in the preaortic region. The first biopsy specimen from the side was called fibrous tissue. To determine operability, the ligament of Treitz was divided to reveal the inferior

mesenteric vein. This was traced to its entrance into the superior mesenteric vein which was surrounded by tumor. A frozen section taken at this place was reported as a malignant tumor, probably of islet cell origin. Although the tumor was obviously inoperable and the bleeding probably from invasion of the duodenum or varices in the region of the tumor, the report of islet cell tumor suggested that we should reconsider the possibility of an ulcer, due to the Zollinger-Ellison syndrome. However, there was no evidence of peptic ulcer and it seemed certain that the mass was the source of the bleeding. I tried to go behind the ligament of Treitz to the posterior wall of the duodenum, but the mass could not be mobilized and was intimately adherent to the duodenum so that an actual ulceration could not be palpated. There were large dilated varices visible over the serosal surface of the bowel near the ligament of Treitz. These indicated obstruction of the veins. There was evidence also of lymphatic obstruction, because the lacteals were dilated even though the patient had been fasting and he had chylous ascites. All together, this was a very distressing situation. Resection of this mass was obviously hopeless. At the present state of surgical technic, we cannot make six or eight anastomoses of the various small branches of the mesenteric arteries and veins. We were forced to close the abdomen without even stopping the bleeding.

DR. SHERRY: There was a note in the operative findings describing 4 L. of chylous ascitic fluid.

DR. HERSHEY: Yes, this was evidence of the lymphatic obstruction produced by this infiltrating malignant tumor.

Dr. Sherry: What was the cause of the gastrointestinal bleeding?

DR. HERSHEY: Probably the varices near the tumor, or invasion of the bowel wall. Because there was blood at the ligament of Treitz and a history of hematemesis, the bleeding must certainly have come from stomach or duodenum. I did not open the stomach and there is, therefore, a faint possibility of a coincident peptic ulcer, but the mass was obviously incurable and we elected not to explore the stomach or small bowel further.

DR. SHERRY: Dr. Spjut, would you show us the results of the frozen section on the biopsy specimen?

DR. HARLAN SPJUT: This section shows the tumor that was encountered. Under the low

power projection the lesion is composed of a small nest of cells set off by rather dense fibrous strands. Under higher power the cells are fairly uniform in regard to nuclear size, but the cell boundaries are quite indistinct. The rather dense fibrous network sets the lesion off in rather discrete nests. This type of pattern of a fibrovascular stroma setting a tumor off into nests suggest that it might be a tumor of endocrine origin. The tumor does not have the appearance suggestive of an adenocarcinoma or a tumor originating in the bile duct. Since it was related to the pancreas as Dr. Hershey has described, with the histologic pattern described, we made the diagnosis of a probable islet cell tumor.

Dr. Scheff: Could this tumor have been a carcinoid?

DR. SPJUT: The problem of differentiating between an islet cell tumor and a carcinoid tumor is commonly encountered when a lesion in this area is found. We cannot always say histologically which is which because they may have exactly the same pattern. The cells have approximately the same staining characteristics and may have the same fibrous pattern setting them off into small nests. Therefore, we cannot say with any great deal of assurance that this could not have been a carcinoid tumor. But I do think we can say with great assurance that this is not a lymphoma.

DR. SHERRY: The features of this case may be summarized as follows: The patient had a large mass, intractable gastrointestinal bleeding, chylous ascitic fluid at operation, a history of recurrent bouts of diarrhea, and yet, in spite of all this the patient had an absence of significant weight loss and had maintained fairly good health until the time of the intractable bleeding. Dr. Shatz, can the entire picture which this patient presents be explained on the basis of an islet cell tumor?

DR. BURTON SHATZ: I presume everyone is familiar with the occurrence of gastric hypersecretion and peptic ulceration in association with a non-functioning islet cell tumor. This syndrome, brought to our attention by Zollinger and Ellison,* has recently received a great deal of attention in the literature. Recently, Ellison†

has reviewed a series of twenty-four cases collected from his own experience and that reported in the literature. The combination of ulceration and islet cell adenoma occurs equally in both sexes. The ages vary from nineteen to seventyeight years with only two patients being under thirty years of age. The symptoms are primarily abdominal pain. However, the pain is usually not typical of the pain associated with peptic ulcer. Diarrhea was present in three cases and was also present in this case. It is believed that the diarrhea is the result of the marked gastric hypersecretion of hydrochloric acid, which acts as a saline cathartic. Diarrhea was the primary complaint which brought the patient to the doctor in the case recently reported by Donaldson et al., * and constant gastric suction regularly caused the diarrhea to subside.

The ulceration of the gastrointestinal tract that occurs in this syndrome is characterized by its atypical location and a tendency for multiplicity. In Ellison's review of twenty-four cases, nineteen patients had a single ulcer, three being in the stomach and nine in the duodenum. However, seven ulcers were in atypical locations; four were in the second duodenum, two in the third duodenum and one in the upper jejunum. Of the five patients who had multiple ulcerations, one had ulcers in the usual location, that is, the stomach and the first portion of the duodenum. However, in three other patients, the ulceration occurred in the second duodenum and upper jejunum. In the fifth patient there were four ulcers; in the epigastroesophageal junction, in the antrum, in the second duodenum, and in the jejunum. Thus, the location of the ulceration is somewhat atypical and there is more of a tendency for multiple ulcerations than one usually encounters.

Another characteristic of the ulceration that occurs in this syndrome is a marked tendency for recurrence. Many of these patients have been operated upon numerous times, and despite subtotal gastric resection ulcerations continue to reappear. Another unusual manifestation is that ulcer complications are the most common cause of death in these patients. While complications of peptic ulcer occur frequently in the patient with ordinary ulcers, they are usually not the

^{*} ZOLLINGER, R. M. and Ellison, E. H. Primary peptic ulcer of the jejunum associated with islet-cell tumors of the pancreas. *Ann. Surg.*, 142: 709, 1955.

[†] Ellison, E. H. Ulcerogenic tumor of the pancreas Surgery, 40: 147, 1956.

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^{*}Donaldson, R. M., Jr., vom Ergen, P. R. and Dwight, R. W. Gastric hypersecretion, peptic ulceration and islet-cell tumor of the pancreas (the Zollinger-Ellison syndrome). Report of a case and review of the literature. New England J. Med., 257: 965, 1957.

cause of death. The indications for surgery in the patients discovered to have the Zollinger-Ellison syndrome, were a palpable mass in two patients, intestinal obstruction in seven, hemorrhage in four, perforation in three, and a combination of all these in another three. In only one patient was intractable pain an indication for surgery; just the reverse of what we see in the ordinary type of peptic ulceration. In the group reported by Ellison only four patients are still alive, and they all had tumors resected. In twelve patients who died of the complications of peptic ulcer disease, the presence of a pancreatic tumor was discovered during life in only one. These islet cell tumors are almost all malignant, only five of the twenty-four having been described as non-malignant. The distribution of the tumors was fairly widespread; most of them being in the body and tail of the pancreas, but occasionally the tumor was in the head of the pancreas. In one patient an islet cell tumor in aberrant pancreatic tissue was found in the stomach.

Hypoglycemia is usually not characteristic of these tumors, although this feature was noted occasionally. The pathogenesis of the ulcers is unknown, although the well recognized hypersecretion and hyperacidity may be contributing factors. The first theory was that these tumors produced glucagon which was thought to stimulate acid secretion by the stomach. Experimental studies have shown that this is not so. Finally, another interesting feature of these cases is the high incidence of adenomas of other endocrine organs. In 25 per cent of these cases, adenomas of the pituitary, the parathyroid and the adrenal glands were also found, and in these latter cases the possibility must be considered that the associated endocrinopathies may have been responsible for the ulcerogenic tendency.

DR. SHERRY: Do you believe this patient had the Zollinger-Ellison syndrome?

DR. SHATZ: One problem bothers me. We have not been able to find an ulcer in this patient either on the roentgenogram or at laparotomy. We have demonstrated a tumor but not the ulcer. The possibility that this tumor is not an islet cell adenoma but perhaps an undifferentiated carcinoma, or a carcinoid, as Dr. Scheff suggested, must be seriously considered. The fact that the patient had cramps and diarrhea for a number of years before the onset of his symptoms would be suggestive of carcinoid. I think that it is impossible to make the diagnosis

on the basis of what we know. If he had a definite ulcer, either seen at surgery or unequivocally demonstrated on roentgenogram, then I would be more inclined to call this an example of the Zollinger-Ellison syndrome.

Dr. Hershey: We examined the stomach, the duodenum and the upper part of the small bowel at surgery and no ulcers were seen. Because of the difficulties previously described, we did not explore the remainder of the small bowel. It is possible that there was a jejunal ulcer present, but very unlikely.

DR. SHERRY: The possibility that our patient does not have an islet cell adenoma as suggested by the pathologist but rather a carcinoid needs to be considered further. Certainly bouts of diarrhea are a common manifestation of the carcinoid syndrome. Dr. Gieselman, would you comment on the carcinoid syndrome?

Dr. Ralph Gieselman: The carcinoid syndrome refers to a clinical picture seen in patients with carcinoid tumors arising in the gastro-intestinal tract, usually with metastases to sites such as the liver, peritoneum or abdominal lymph nodes. The symptoms include episodes of flushing, palpitation, abdominal pain of a colicky nature or diarrhea. These events may occur singly or in combination. In addition to abdominal masses or an enlarged firm liver, which signify the metastases, heart murmurs usually from the tricuspid or pulmonary valve area may be noted on physical examination.

Most of the widespread biological effects have been traced to the 5-hydroxytryptamine or serotonin produced by these tumors which arise from the enterochromaffin cells of the gastrointestinal tract. The mechanism of the cardiac changes and valvular thickenings responsible for the murmurs remains in doubt.

The endocrine picture caused by these tumors is seen only when tumor tissue is drained by extraportal veins. Serotonin is probably broken down in the liver by an enzyme, amine oxidase, into 5-hydroxyindoleacetic acid. The latter is pharmacologically inactive and excreted into the urine. The presence of this urinary metabolite allows for a rather simple laboratory diagnosis of the syndrome, but since its excretion may vary from day to day, it may be necessary to examine more than one twenty-four-hour urine specimen.

DR. SHERRY: Is the diarrhea related to increased levels of circulating serotonin?

Dr. Gieselman: Bouts of diarrhea usually

imply that there are metastatic lesions, and we are observing a systemic effect. One can postulate that in an actively secreting tumor, serotonin may stimulate the adjacent myenteric plexus and this may be sufficient to alter gastrointestinal motility. However, in our experience, the patients with diarrhea have always had metastases.

I think this case is compatible with carcinoid although there is little more to be said for one diagnosis than for the other.

DR. SHERRY: Dr. Scheff, is it at all possible that our patient does not have a neoplasm in his pancreas? Some patients with chronic pancreatitis may have masses in the pancreas which can simulate a neoplasm and lead to a mistaken diagnosis on frozen section. Our patient not only had diarrhea, which could suggest steatorrhea, but fasting hyperglycemia as well. Could this all be chronic pancreatitis?

Dr. Scheff: This is always a possibility. However, chronic pancreatitis involves the entire pancreas and particularly the body or tail, unlike the description given here. I would doubt that there is a primary neoplasm in the pancreas at all; if there were, one would have expected much more pain than this patient ever displayed, and considerable weight loss. The absence of pain, weight loss or a palpable mass would make me suspect that the pancreas was not involved. More suggestive to me, is a lesion arising in the small bowel with metastatic retroperitoneal nodes all matted together. That is the reason I thought of carcinoid. The latter can go on for years producing minimal or only vague symptoms.

DR. Hershey: Concerning the question of pancreatitis, the remainder of the pancreas was entirely normal. The mass, unquestionably a malignant tumor, was actually in the mesentery. However, if it had not been for the frozen section diagnosis of pancreatic carcinoma, my gross diagnosis would have been a retroperitoneal lymphoma involving the mesentery.

DR. SHERRY: Dr. Moore, patients with lymphomas may have a history of lower abdominal discomfort and diarrhea. These symptoms may be relatively benign from a clinical standpoint and yet the lymphoma may grow slowly, obstruct lymphatics and invade the bowel wall. I am a little shaken by the surgical pathologist who excludes this from consideration. Do you believe the possibility of a retroperitoneal lymphoma which has extended anteriorly must still be entertained?

DR. CARL MOORE: Dr. Sherry, you and I talked before the conference and agreed that there was nothing in this story which would be incompatible with lymphosarcoma. Hodgkin's disease would be unlikely because of the absence of systemic manifestations. Everything else could fit with lymphosarcoma but since one cannot ignore the pathological findings during surgery, I would be inclined to exclude the possibility of lymphoma.

DR. SHERRY: Dr. Nickel, is there anything else we should consider?

DR. NICKEL: No. I believe it is impressive that this man, in the two months prior to his death, actually had gained about 5 pounds of weight and his diarrhea was virtually controlled by simple measures. His blood count had always been normal, and blood sugar studies made by Dr. Scheff and myself were always normal. With the information we have, it is surprising that he did as well for so long with a malignancy of any kind.

DR. MOORE: Dr. Sherry, would you explain the fasting blood sugar of 197 mg. per cent observed at the time of admission?

DR. SHERRY: It is possible that this man might have had a mild diabetes with an abnormal glucose tolerance and that the stress of bleeding may have thrown him out of control. On the other hand, one would be tempted to try to relate the hyperglycemia to the pancreas. From the data presented, I am unprepared to try to explain it any further. Dr. Recant do you have any additional thoughts about the elevated blood sugar?

DR. LILLIAN RECANT: Is there any possibility that this was an alpha cell tumor? Aside from an elevated blood sugar there are no data on which to base this possibility.

DR. SHERRY: What about alpha cell tumors in adults? I thought they were extremely rare. Certainly the Zollinger-Ellison syndrome initially was believed to be due to an alpha cell tumor, but this view was soon discarded. Have true glucagon-producing alpha cell tumors of the pancreas been described?

DR. RECANT: Perhaps Dr. Lacy might be able to answer that question. There have been reports of pathologic material that looked like alpha cell tumors, but I doubt that glucagon has ever been isolated from any of these.

DR. PAUL LAGY: That is quite correct. There have been no reported cases in which glucagon has been extracted from an islet cell tumor.

DR. SHATZ: It is of interest to point out that Eiseman and Maynard* looked for the presence of increased amounts of glucagon or glucagon-like substances in the blood of patients with the Zollinger-Ellison syndrome but were unable to demonstrate this.

DR. SHERRY: I gather from the discussion that some of you believe the patient had a non-insulin-producing islet cell adenoma with the Zollinger-Ellison syndrome while others believe a malignant carcinoid more likely. The possibility of some other type of neoplastic mass probably arising from the mesentery has not been completely excluded. My own vote goes for a malignant carcinoid.

PATHOLOGIC DISCUSSION

DR. JOE W. GRISHAM: The major gross pathologic lesions were observed in the abdominal cavity of this patient. Approximately 400 ml. of sanguineous, slightly cloudy fluid was present in the abdomen. The subserosal vessels of the small and large intestine and the mesenteric vessels were markedly dilated. This change was most evident in the wall of the small intestine. A firm, circumscribed tumor (10 by 5 by 5 cm.) was present in the root of the mesentery of the small intestine. The tumor mass was completely isolated from the pancreas although it was adherent to the serosa and underlying circular muscle of the third portion of the duodenum. The duodenal mucosa was not ulcerated or eroded. The superior mesenteric artery and vein were imbedded in the tumor and the distal branches of the superior mesenteric vein were severely dilated. The cut surface of the tumor was soft in its central portion and appeared yellowish brown. It was encased by a thick fibrous capsule (5 mm.). The gastrointestinal tract contained 1 to 2 L. of fluid and clotted blood. The mucosa of the entire gastrointestinal tract appeared normal except for the congestion of the blood vessels in the small intestine. A small (1 cm.), yellow submucosal tumor was observed in the terminal ileum approximately 15 cm. from the ileocecal valve. The serosal surface of the intestine was puckered in this area. A second small (5 mm.), yellowish submucosal tumor was also present in this area. The tumor had not metastasized to the liver and

no tumor masses were found outside the areas drained by the portal vein. The valves of the heart appeared normal. The liver, kidney, spleen and lung were markedly crepitant. This was apparently due to gas produced by clostridium bacilli which were cultured from the blood and liver at autopsy.

DR. PAUL E. LACY: Microscopically, the tumor in the mesentery was composed of nests and strands of cells isolated by dense, fibrous connective tissue. (Fig. 2.) The tumor cells are small and have a relatively larger amount of pink-staining cytoplasm. In some areas, pseudorosettes were observed and mucoid material was demonstrable in the center of the rosettes. (Fig. 3.) These microscopic features are indicative of a carcinoid. A microscopic metastatic focus of tumor was found in the pancreas. Granules were not demonstrable with aldehyde fuchsin in the tumor cells which was additional evidence that the tumor did not originate from beta cells. The islets of Langerhans in the same section contained a normal complement of beta granules. An argentaffin reaction was also performed on the tumor cells. Scattered black granules were produced in the tumor cells although the reaction was not entirely satisfactory. The cells were not argyrophilic since they could not be impregnated with reduced silver. Alpha cells are not argyrophilic whereas argentaffin cells of the intestine react positively with the argentaffin stain. These histochemical observations also indicate that the tumor originated from argentaffin cells and not from alpha

Electron microscopic studies were also made on the biopsied specimen of the tumor. (Fig. 4.) Distinct secretory granules are present in the cytoplasm of the tumor cells. The granules are enclosed by smooth membranes similar to secretory granules of other endocrine cells. Previously it was believed that the argentaffin granules were artifacts which were produced as a result of fixation in formalin. The recent electron microscopic studies of Christie* on the normal argentaffin cells of the intestinal tract clearly indicate that these granules are not artifacts of fixation. It is also apparent from the electron microscopic appearance of these tumor cells that true secretory granules exist in these cells.

^{*} EISEMAN, B. and MAYNARD, R. M. Non-insulin producing islet-cell adenoma associated with progressive peptic ulceration. *Gastroenterology*, 31: 296, 1956.

^{*} Christie, A. C. A study of the Kultschitzky (argentaffin) cell with the electron microscope after fixation by osmium tetroxide. *Quart. J. Microscopical Sc.*, 96: 295, 99, 1955.

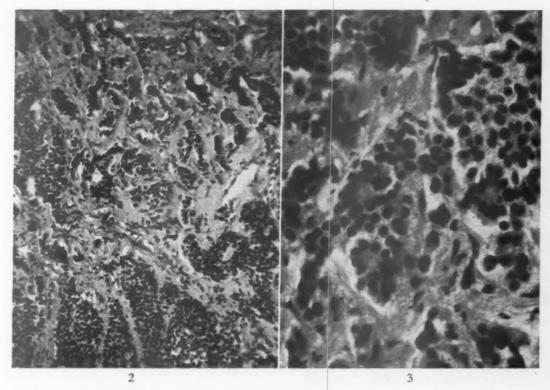


Fig. 2. The metastatic carcinoid in the mesentery is illustrated. The tumor cells are arranged as nests and columns of small cells isolated by surrounding bands of dense fibrous tissue. This same histological pattern was present in the primary carcinoid of the ileum. Hematoxylin and eosin stain.

Fig. 3. Numerous pseudorosettes are present in the tumor. The cells have a radial arrangement around an amorphous material which is present within the centers of the pseudorosettes. Hematoxylin and cosin stain.

The cytoplasm of the tumor cells also contains a moderate amount of ergastoplasm, distinct mitochondria and scattered droplets of lipochrome pigment. In normal cells, the nuclei are bounded by two distinct membranes which are closely apposed. It is interesting, that in many of these tumor cells, the outer nuclear membrane is widely separated from the inner membrane. This separation did not extend around the entire circumference of the cell but occurred only in focal areas. The significance of this unique appearance of the nuclear membranes is not apparent at the present time. Bundles of collagen fibers were observed immediately adjacent to the plasma membranes of many of the tumor cells. By electron microscopy, the tumor cells could also be differentiated from alpha cells on the basis of certain criteria. The argentaffin granules of this tumor are distinctly different from alpha cell granules of the normal human pancreas. The alpha granules are larger, denser and have a smooth round contour whereas the argentaffin granules are less dense and more irregularly shaped. In addition the

nuclear membranes of alpha cells are closely apposed whereas they were widely separated in some of the tumor cells.

The larger nodule observed in the ileum was composed of nests and columns of small cells similar to those present in the large metastatic area in the mesentery. The tumor cells extended from the mucosa, through the muscular wall of the ileum to the serosa. This nodule was apparently the primary site of origin of the carcinoid. The second smaller nodule in the ileum was also a carcinoid but the tumor cells were limited to the mucosa of the ileum. Numerous rod-shaped bacteria were present in the blood vessels of the heart, liver and lungs. These were apparently the clostridium bacilli which were cultured at autopsy. The bacteria were not accompanied by an inflammatory reaction so they probably represent a terminal infection with some continued growth of the bacteria after death.

The gastrointestinal bleeding apparently originated from the severely congested vessels of the small intestine. The congestion was

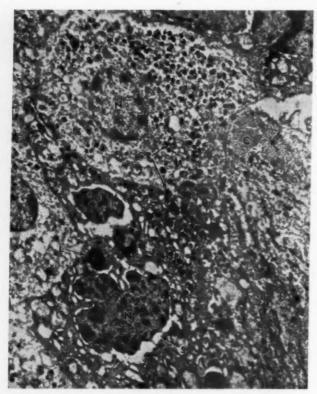


Fig. 4. Electron micrograph of tumor cells of the carcinoid. In some of the cells the nuclei (N) have spaces (S) around them. They are formed by focal areas of separation of the inner and outer nuclear membranes which produce focal, dilated spaces around the nuclei. Distinct secretory granules (GR) are present in the cytoplasm. With higher magnification, a distinct membrane can be observed around most of the secretory granules. Occasional lipochrome bodies (L) are present in the cytoplasm. Cross sections of collagen fibers (C) can be seen immediately adjacent to the tumor cells.

secondary to the obstruction of the superior mesenteric vein by the large tumor mass. We were unable to find any gross or microscopic evidence of ulceration in the gastrointestinal tract.

The final anatomical diagnoses are carcinoid tumors of the terminal ileum (one 1 by 1 cm. and one .5 by .5 cm.) with invasion through the muscle of the intestinal wall; metastatic carcinoid in mesenteric lymph nodes, root of the mesentery (10 by 5 by 5 cm.), in peripancreatic lymph nodes and in the pancreas (history of biopsy and diagnosis of carcinoid tumor at surgery-pathologic report No. 58-7442); obstruction of the superior mesenteric artery and vein by the mesenteric tumor mass; dilatation of the mesenteric and serosal vessels; midline incision, 18 cm., of the anterior abdominal wall, unhealed, sutured, (history of exploratory laparotomy performed on the day prior to death); acute necrotizing proctitis (gram-positive cocci and bacilli in exudate); gram-positive sporebearing rods in the lungs, heart, spleen, liver, kidneys and tumor mass; crepitance of all viscera with gas present in all blood vessels (gram-positive rod on smear and culture); blood (clotted and fluid) present in the entire gastrointestinal tract (estimated contents, 1 to 21 cc.), (history of bleeding per rectum, with transfusion); arteriosclerosis of the aorta, coronary arteries, advanced; of the splenic, renal and mesenteric, moderate; sclerosis of the anterior leaflet of the mitral valve; calcified subpleural nodule, upper lobe of the left lung; calcified hilar nodes; arteriolar nephrosclerosis, moderate; chronic cholecystitis with cholelithiasis (twenty-three mixed stones, all less than 1 cm. in diameter in the gallbladder); nodular hyperplasia of the prostate; and atrophy of the testicles.

Cardiopulmonary Insufficiency Associated with Myotonic Dystrophy*

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ALTHOUGH weakness of the respiratory muscles and diaphragm has been observed in patients with myotonic dystrophy, little attention has been given to the early signs of respiratory insufficiency in these persons. Susceptibility to bronchitis and pneumonia were noted by early workers, but more recently Thomasen and others have commented upon the presence of somnolence, lethargy and acrocyanosis [1–5]. To our knowledge, Benaim and Worster-Drought were the first to report detailed studies of pulmonary function in a patient with myotonic dystrophy associated with impaired diaphragmatic movements, hypoxemia, hypercapnia, somnolence and obesity [6].

The present report summarizes the clinical and laboratory observations in a young man with myotonic dystrophy who showed marked somnolence, cyanosis, Cheyne-Stokes breathing and mild obesity.

CASE REPORT

N. S., a thirty-one year old, white, unmarried traveling salesman was admitted to the Durham Veterans Administration Hospital on December 20, 1957, with the complaints of muscular weakness and enuresis. The patient recalled that as a youth he could not compete with his friends in tests of hand strength. He dated the onset of distinct muscular weakness at about the age of twenty. At that time, while working as a salesman, he had noted increasing difficulty in climbing stairs and frequently had to rest on the landings. He had noted no further weakness until the age of twenty-three when he became acutely aware of hand weakness while serving as a pallbearer. He also observed that he could not easily relax his grasp and on several occasions while "Indian wrestling" he noted that his hand grip tended to "stick." The symptoms of weakness slowly progressed and he became unable to dance, to rise from a squatting

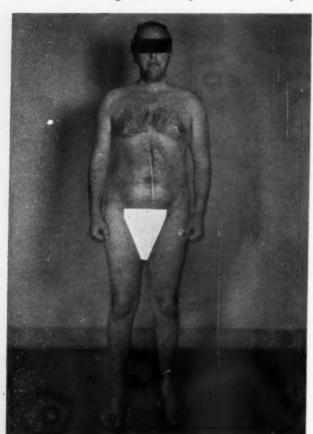
position, to walk on his toes or heels, or to walk up a flight of stairs without using his arms to assist himself.

At the age of twenty-five frontal baldness had developed which progressed during the next several years to involve the temporal areas. At this time, he was found to have a cataract of the right eye which necessitated removal of the lens two years later. He did not note any alterations in facial appearance or weakness of the jaw or neck muscles.

The patient's urinary symptoms began at age twenty-three when recurring enuresis of a month's duration developed once or twice a year. In the summer before admission, however, enuresis had become much more frequent and had occurred at least once or twice each night. This became so severe and frequent that hotels at which he had stayed during his traveling denied him accommodations. The patient had to void as often as seven to ten times during the day, often with considerable urgency. Occasionally he had daytime incontinence, but no difficulty initiating the urinary stream. There was loss of libido during the six months prior to admission.

He also gave a history of somnolence dating from late adolescence. At this time while in the Army, he frequently fell asleep on guard duty and often slept when off duty and on weekends. He was considered by his friends to have "sleeping sickness" because of his sleep habits. In his early twenties, he often fell asleep while driving a car and as a result had two serious accidents. On three other occasions the car was driven into a ditch or across a field by the side of the road when he fell asleep at the wheel. The patient attempted to keep awake while driving by taking stimulants, turning on the car radio at full volume or holding his head out the window. He frequently became sleepy while watching television, listening to the radio, reading or during church services. While at home he often napped for as long as thirty to sixty minutes after breakfast and lunch. His nocturnal sleep was sound and he slept through the alarm set to arouse him to get up to void. He had frequent dreams but no hypnagogic hallucinations. There was no history to

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Ftg. 1. A photograph of the patient showing the myopathic facies, frontal balding and slight obesity.

suggest cataplexy. Frequently he had symptoms of sleep paralysis which occurred just prior to his falling asleep.

The patient's weight prior to his Army service at age seventeen was 165 pounds. On discharge from the Army two years later he weighed 180 pounds and subsequently averaged 200 to 230 pounds.

While in the Army the patient was told he had an increased amount of blood, enough to give several transfusions. On one occasion while donating blood a year prior to his hospitalization he was told that his blood was excessively thick.

In 1945, the patient was hospitalized for hepatitis manifested by jaundice, anorexia and dark urine. Following this recurrent attacks developed at intervals of six months, of cramping abdominal pain, vomiting, sallow complexion and dark urine. These episodes were unrelated to exercise.

There was no family history of a similar type of muscular weakness. The patient's father died at age thirty-nine of cerebral hemorrhage and two siblings died of accidents. One brother is living without evidence of muscle disease. The patient's sister, who weighed 256 pounds, died at age thirty-four with bronchopneumonia and cardiac dilatation diagnosed at autopsy. There was also fatty infiltration in the right ventricle but no skeletal muscle was examined. The

patient's sixty-four year old mother showed no evidence of neuromuscular disease.

Physical examination revealed an alert, intelligent and cooperative man. He was 71 inches tall and weighed 213 pounds but appeared somewhat obese with a centripetal distribution of fat. (Fig. 1.) There was slight cyanosis of the lips, buccal mucosa and nail beds, without clubbing of the fingers or toes. Marked frontal and temporal baldness was present. The blood pressure was 120/90 mm. Hg in each arm. When the patient was relaxed Cheyne-Stokes respirations were observed. (Fig. 2.) The heart rate was 120 with a grossly irregular rhythm. The breath sounds were clear but fine inspiratory rales were present in the bases of both lungs. The heart did not appear enlarged and no murmurs were heard. The abdomen was somewhat obese. The liver and spleen were not enlarged and no masses were palpable. The testes were small but not atrophic. There was abundant body hair with a male distribution. Slight pretibial edema was present bilaterally.

The neurologic examination showed hollowed temporal areas bilaterally and an expressionless facies. There was marked ptosis and weakness of the orbicularis oculi. He was unable to keep the eyes shut against resistance. The other facial muscles were also weak and the patient could not grimace to show his teeth. There was postoperative absence of the right lens. His speech was somewhat dysarthric with a nasal quality. There was no weakness or atrophy of the sternocleidomastoid or masseter muscles. There was no muscle atrophy of the limbs. The strength of the arms was good but the grip was moderately weak in both hands. He was unable to relax his grip quickly after sustained contraction but with repeated contractions relaxation improved. Percussion of the tongue and the thenar areas produced localized myotonic contractions. The patient was unable to stand on his toes or walk on his heels. He had weakness of flexion of his legs and was unable to step up on a chair with either leg. The deep tendon reflexes were absent in all extremities. Sensory examination was normal. The patient had a broad-based gait with

a slapping quality. Laboratory examination showed hemoglobin values ranging between 17.6 and 19.1 gm./100 ml., the red blood cell count was 5.53 million/cu. mm. and the volume of packed red cells averaged 52 ml./100 ml. The red cell indices were normal and the red cells appeared normochromic and normocytic. The reticulocyte count was 0.5 per cent. The white blood cell count ranged from 5,300 to 7,750/cu. mm. and the differential count revealed 58 polymorphonuclear cells, 26 lymphocytes, 12 monocytes and 4 eosinophils per 100 cells. A platelet count was normal. The urine contained no sugar, protein, porphobilinogen, or excessive urobilinogen, and microscopic examination revealed no abnormalities. Concentrations of calcium, phosphorous, sodium, chloride, urea, sugar, and

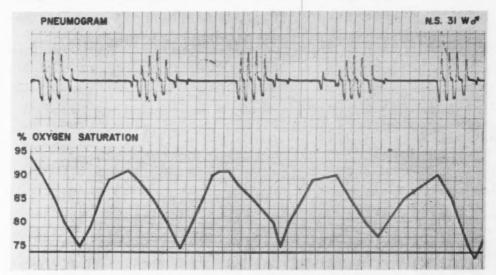


Fig. 2. Correlation of periodic respiration with oximetric (ear) readings of arterial oxygen saturation.

cholesterol in the blood were normal. The serum potassium concentration was 4.9 mEq./L. The total serum protein was 6.5 gm./100 ml. with 4.8 gm. of albumin and a normal electrophoretic pattern. There was 13 per cent retention of bromsulphalein in forty-five minutes. The serum bilirubin which was all indirect reacting ranged from 0.45 to 0.7 mg. per cent/ 100 ml. The basal metabolic rate was -22 per cent on two occasions. With the patient on a regular hospital diet the creatine excretion was 154 mg., and the creatinine excretion was 1,324 mg./twenty-four hours in a urine volume of 2,200 ml. Microscopic examination of a biopsy specimen of the liver revealed numerous fat-filled hepatic cells in the central zones. One mid-zone area was infiltrated by lymphocytes and a few polymorphonuclear cells but there was no fibrosis or pigment. Microscopic examination of a biopsy specimen of the left gastrocnemius muscle showed hyalinization and necrosis of muscle fibers with fibrosis and fatty replacement. (Fig. 3.) There were increased numbers of muscle cell nuclei. This was a diffuse process without localization to motor units.

Roentgenologic examination of the chest showed a cardiothoracic ratio of 17/31 cm. and increased pulmonary vascular markings. Fluoroscopic examination of the chest suggested that the cardiomegaly was predominately due to left ventricular enlargement. The diaphragms moved about 3 cm. on inspiration. The initial descent was rapid but was followed by jerky, irregular movements which produced little displacement. The diaphragms ascended slowly and haltingly and the entire cycle was delayed.

Electrocardiograms showed variation between sinus rhythm, with atrial and ventricular premature beats, and atrial fibrillation. There was left axis deviation and an incomplete right bundle branch block. The PR interval was 0.20 second. Conversion of the atrial fibrillation was attempted with the administration of quinidine but on one occasion hypotension resulted and on another, paroxysmal ventricular tachycardia ensued. Spontaneous conversion to sinus rhythm occurred and was maintained with quinidine therapy.

Pulmonary function studies showed a decrease in vital capacity (2,460 ml.), small expiratory reserve volume (711 ml.) and small total lung capacity (3,604 ml.). (Table I.) The maximal breathing capacity was also decreased with a value of 72 L./minute as compared with a predicted value of 151 L./minute. An analysis of arterial blood gases revealed low oxygen saturations, varying from 80.6 to 89.8 per



Fig. 3. A photomicrograph of the gastrocnemius muscle showing a few degenerated muscle fibers containing many nuclei separated by fibrous connective tissue. Hematoxylin and eosin × 110.

TABLE I
PULMONARY FUNCTIONS AND ARTERIAL BLOOD GAS VALUES

	1-2-58	3-5-58	B & W-D*	Normal Values
Inspiratory reserve volume (ml.)	837	1,030	640	3,100
Expiratory reserve volume (ml.)	711	650	130	1,200
Vital capacity (ml.)	2,460	2,380	1,130	4,800
Residual volume (ml.)	1,139	590	970	1,200
Functional residual capacity (ml.)	1,850	1,240	1,100	2,400
Total lung capacity (ml.)	3,604	2,970	2,100	6,000
Residual volume/total lung capacity × 100 (%)	31	20	46	20
Tidal volume (ml.)	340	450	316	500
Frequency (respirations/min.)	18	13	21	12
Minute volume (L./min.)	6.1	5.9	6.9	6.0
Alveolar ventilation (L./min.)	3.0	3.7	2.3	4.2
Maximal breathing capacity (L./min.)	72	72	45	151
O_2 saturation (air) (%)	80.6	84	84.4	97
O ₂ saturation (100 per cent O ₂) (%)	96.2			100
CO ₂ tension (air) (mm. Hg)	58.4	57	67.4	41
CO ₂ tension (100 per cent O ₂) (mm. Hg)	73.2			41
pH	7.32	7.35	7.29	7.4
Weight (pounds)	213	207	206	
Height (inches)	71	71	63	

RESPONSE TO 5 PER CENT CO2 INHALATION

		Patient		Normal [14]		
*	Rest	5 Min.	10 Min.	Rest	5 Min.	10 Min
Frequency	13	17	18	14	16	18
Minute ventilation (L./min.)	6.3	10.3	11.0	7.4	21.5	24.1
CO ₂ tension (mm. Hg)	60.3	71.2	71.5	45.2	57	56
O ₂ saturation (%)	87	94	97	96	97	97

* Patient reported by Benaim and Worster-Drought [6].

† Values obtained from data by Comroe [19].

cent. During Cheyne-Stokes breathing a greater variation was recorded by oximetry. (Fig. 2.) Oxygen saturation increased to 96 per cent after five minutes of inhalation of 100 per cent oxygen. The carbon dioxide tension of arterial blood was elevated, ranging from 56 to 60 mm. Hg, and the pH ranged from 7.30 to 7.35. Helium washout showed a rapid but irregular slope, probably due to the periodic periods of apnea. The ventilatory response to 5 per cent carbon dioxide inhalation was slightly decreased.

Venous catheterization of the heart showed elevated pulmonary "wedge" and pulmonary artery pressures and a low cardiac index (2.0 to 2.4 L./minute/sq. M.) at rest. (Table II.) Exercise increased oxygen consumption 123 per cent and widened the A-V oxygen difference, mainly by increasing the arterial oxygen saturation and produced an increase in cardiac index (3.3 L./minute/sq. M.). The low cardiac output did

not change after digitalis was administered. The right ventricular end diastolic pressure was 4 mm. Hg.

On cystometric examination the patient experienced a need to void with 100 ml. in the bladder. A sensation of fullness was experienced at 200 ml. and maximal bladder filling occurred at 250 ml. There was a normal urinary stream. Cystoscopic examination showed only hyperemia and edema of the trigone and ureteral orifices. Intravenous pyelograms revealed normal collecting systems in both kidneys. Roentgenographic examination of the gastrointestinal system and gallbladder failed to show any abnormalities.

Electromyography of several forearm and hand muscle groups, including the brachialis, biceps, extensor pollicus brevis and the flexor carpi radialis, showed a pattern of sustained firing with delayed relaxation typical of myotonia.

TABLE II
PULMONARY VASCULAR PRESSURES, CARDIAC OUTPUT AND BLOOD GASES

State of Subject Wedge Mean	Pulmonary Vascular Pressures							Oxygen Saturation Per cent	
	Wedge	Artery		Oxygen Consump- tion (ml./min.)	(A-V) O2 (vol. %)	Cardiac Output (L./min.)	Cardiac Index (L./min./sq. M.)	Mixed	Brachial
	Mean mm. Hg	S/D mm. Hg	Mean mm. Hg	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,				Venous	Artery
Rest	20	35/22	27	230	5.02	4.6	2.1	62.5	86.1
Exercise	27	42-70/35-40	45	512	7.26	7.0	3.3	60.2	94.4
Rest	15	30-44/17-30	30						
O2 inhalation	22	27-43/15-26	25	235	5.30	4.4	2.0	75.1	100
Rest	22	27-40/15-25	27	***	****	***		****	
Acetylcholine	13	24-32/15-21	22	217	4.32	5.0	2.3	59.6	80.3
Rest	12	31-39/16-27	28	222	4.34	5.1	2.4	59.2	80.0
Quinidine and digitalis	17	19-35/12-20	21	237	5.34	4.4	2.0	61.6	87.2

Following discharge from the hospital the patient continued to have enuresis despite medication with methantheline. His somnolence also persisted after usual doses of amphetamine. Quinidine therapy was associated with a normal cardiac rhythm and seemed to decrease the myotonic response of his muscles. While on a 1,000 calorie diet he lost 6 pounds of weight but showed little change in his blood gas values or pulmonary function studies. Six weeks after leaving the hospital, the patient showed progressive weakness of the arm and leg muscles.

COMMENTS

There is little doubt as to the diagnosis of myotonic dystrophy in this patient. He exhibited the classic clinical manifestations of baldness, cataracts, myotonia, muscular dystrophy and reduced sexual function [1]. Histologic examination of skeletal muscle and the electromyographic findings confirmed the clinical diagnosis. The cause of the severe enuresis remains unexplained. To our knowledge, involvement of smooth muscle such as the urinary bladder or sphincter, by the dystrophic process has not been observed. There was no evidence to suggest a lesion of the spinal cord or lumbosacral nerves.

In addition to myotonic dystrophy the patient showed evidence of cardiopulmonary insufficiency, including somnolence, Cheyne-Stokes respiration, cyanosis, polycythemia, hypercapnia, hypoxemia and pulmonary hypertension. This particular group of manifestations has in recent years been recognized as being caused by alveolar hypoventilation [7,8]. If patients with primary lung disease are excluded, there remains a

heterogenous group of patients in whom hypoventilation is associated with inadequate bellows action of the chest. In a few instances, alveolar hypoventilation may have resulted from insufficient ventilatory drive as a result of a lesion in the respiratory center of the brain [9]. In the majority of cases, however, there was a failure of the thoracic cage or diaphragm to ventilate the lungs adequately. Conditions which have been observed to interfere with the bellows function of the chest wall are extreme obesity, kyphoscoliosis and widespread pleural thickening [7,10].

Patients with Guillain-Barré disease, poliomyelitis and other motor neuron lesions have been found to have sufficient weakness of the chest muscles to produce a similar type of pulmonary insufficiency [11-13]. It would seem reasonable to include in this category patients with muscular dystrophy. Both the case described by Benaim and Worster-Drought as well as the patient presented in this report have evidence of alveolar hypoventilation caused by myotonic dystrophy of the respiratory muscles. The diaphragms of both patients showed diminished excursions fluoroscopically with unusual jerking movements on ascent and descent. In addition, both our patient and that reported by the English workers had reduction in total lung capacity, vital capacity and maximal breathing capacity. Studies in our laboratory on four other patients with myotonic dystrophy revealed that one of them had retention of carbon dioxide and a reduction of oxygen saturation [14]. All, however, showed a 20 to 40 per cent decrease in maximal breathing capacity and three had a reduced total lung

volume. These were all young persons in whom there was no evidence of lung disease. It is reasonable, therefore, to infer that the derangements in pulmonary function were due to their

inability to ventilate adequately.

It can be postulated that the decrease in total lung capacity and alveolar ventilation which produced this degree of hypercapnia and hypoxemia in our patient reduced the volume of the pulmonary vascular bed and was reflected as an increased pulmonary wedge pressure. The sum of the effects of anoxemia and increased resistance of the pulmonary vascular bed increased the work load of the right ventricle and raised the pressure in the pulmonary artery. The hypervolemia associated with polycythemia and possibly a toxic effect of hypoxemia and hypercapnia on the myocardium may have impaired cardiac compensation. The possibility that myocardial reserve has been further lessened by dystrophic involvement of the heart is suggested by the abnormalities of conduction, rhythm and electrical position. There have been only a few postmortem examinations of the heart in this condition but various electrical alterations have been described, such as delayed A-V conduction, low amplitude of QRS, slurring of P waves, varying electrical conduction and occasionally incomplete right bundle branch block or atrial fibrillation [15-17]. In the present patient the sum of these alterations produced manifestations of congestive heart failure.

The degree of obesity displayed by our patient and the patient of Benaim and Worster-Drought is not usually associated with an elevation of carbon dioxide tension or with reduction in oxygen saturation [14]. It seems unlikely that this factor alone could be the cause of such extreme changes in blood gases as observed in these two patients. The etiology of somnolence in our patient as well as in others with a similar cardiopulmonary syndrome cannot be satisfactorily explained. It has been presumed to be of hypothalamic origin, or related to the narcotic effect of carbon dioxide retention on the cerebral cortex. Neither explanation is wholly acceptable since somnolence usually disappears in the obese subjects with weight reduction and patients with chronic emphysema often have greater levels of carbon dioxide retention without signs of sleep disturbances. The relationship of mental alertness and respiratory function has aroused considerable interest in recent years.

We have found that an elevation of carbon dioxide tension and reduction in oxygen saturation appears with the onset of drowsiness prior to natural sleep and similar alterations have been found in narcoleptic patients while awake [18]. Undoubtedly respiratory movement produces some type of alerting effect in an otherwise resting subject. When this is decreased by factors retarding the movement of the chest wall, sleepiness may appear.

The Cheyne-Stokes respiration observed in our patient may be related to the appearance of somnolence and in this respect is similar to the phasic breathing observed in some normal peo-

ple during sleep.

Proof of our hypothesis that the hypoventilation syndrome in this patient is due to a dystrophic process of the diaphragm and intercostal muscles is not possible. Many gaps remain in our understanding of the pathogenesis of this cardiopulmonary disturbance.

SUMMARY

A thirty-one year old man with a long history of myotonic dystrophy was observed to have somnolence, cyanosis, Cheyne-Stokes breathing and a cardiac arrhythmia. Cardiopulmonary function studies revealed a decrease in vital capacity and total lung volume and a reduction in maximal breathing capacity. In addition hypercapnia, hypoxemia, and pulmonary hypertension were observed. It is suggested that dystrophy of the respiratory muscles and possibly of the myocardium in this patient produced the syndrome of alveolar hypoventilation.

Acknowledgment: We are indebted to Mrs. Mary Pike and Miss Corinna Thomas for their invaluable assistance.

ADDENDUM

Since this manuscript was submitted a report by Bashour, Winchell and Reddington [20] has come to our attention. These workers reported on a fifty-seven year old man, bedridden with myotonic dystrophy for several years, who showed cyanosis, small lung volumes and an elevated pulmonary artery pressure.

Six months after the first observations, June 1958, repeat studies were obtained on our patient. Although the blood gases were nearer normal than initially the oxygen saturation on room air was only 89.7 per cent and the CO2

tension was 55.6 mm. Hg. The lung volumes had decreased slightly as reflected by a vital capacity of 2,140 ml. The maximal breathing capacity was 63 L./minute and the minute volume was 6 L. on room air and 5 L. when 100 per cent oxygen was breathed. The patient's condition was symptomatically unchanged except for some decrease in somnolence.

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Idiopathic Hypercalcemia*

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T is becoming apparent that there are at least two varieties of idiopathic hypercalcemia: a chronic, more severe form which was first described by Butler and Fanconi [1-4] and a transitory, milder type which was described by Lightwood [5] and Payne [6]. The severe form of idiopathic hypercalcemia has been described as consisting of the triad of (1) hypercalcemia associated with azotemia, (2) osteosclerosis, and (3) physical and mental retardation. (Table 1.) This severe form usually pursues a progressively downhill course, a sizeable number of patients succumbing within the first five years of life. The milder variety is characterized by an elevated serum calcium accompanied by the symptoms usually associated with hypercalcemia, i.e., anorexia, vomiting, constipation, polyuria and muscular hypotonia. This type is not accompanied by osseous changes or physical and mental retardation and it has a distinct tendency to remit spontaneously after several months.

For the past four years we have had under observation a patient who had hypercalcemia, azotemia, and unusual roentgen findings of the skeleton since the age of ten years, and who has recently been found to conform in many respects to one of the initial cases described by Fanconi et al. Since this patient has survived to the age of

TABLE I

Features	Benign	Severe		
Course	Transient, self- limited	Protracted		
Facies		"Elfin"		
Bones		Osteosclerosis		
Heart		Murmur		
Blood pressure		Elevated		
Mental development		Retarded		
Prognosis		Findings per- sist, or death		

puberty and is not mentally or physically retarded, it is probable that he represents an intermediate form of this syndrome. Moreover, this appears to be the oldest patient thus far reported with the syndrome of idiopathic hypercalcemia. Included is a serial presentation of the skeletal roentgen changes showing a tendency toward improvement. A summary of the previously reported cases is presented and differences between them and the present case are discussed.

CASE REPORT

G. K., at the age of ten and a half years, was admitted to The Mount Sinai Hospital on May 26, 1953, for diagnostic study. He was anorexic and had gained weight slowly; he was retarded in height and (at another institution) had been noted to have signs of renal dysfunction.

The patient, who weighed 4,000 gm. at birth, was delivered by cesarean section on January 7, 1943. Two previous pregnancies of the mother had resulted in full term stillborn infants; the infants were said to have been "too large and were crushed during delivery." Seven months after delivery of our patient his mother died following a blood transfusion necessitated by "general debility." Also of interest in the family history is the fact that a kidney stone developed in the patient's father in 1953. The latter's serum calcium, phosphorus and alkaline phosphatase determined at that time were normal.

Although the patient's neonatal course was normal, it soon became apparent that he had a poor appetite and that his gain in weight and growth in height were retarded. Polyuria and polydypsia were also noted. Mental and motor achievements appeared to keep pace with his age. According to his father, the child was given the usual vitamin supplements, with no excess of vitamin D. At four years of age these symptoms became especially noticeable but it was not until the child was nine and a half years old that the urine was examined and revealed a trace of albumin, pyuria and a low specific gravity.

Three months before admission to The Mount Sinai Hospital the child was admitted to another institution for study. There the urinary findings were confirmed. Elevated blood urea nitrogen and serum creatinine concentrations were found. Roentgeno-

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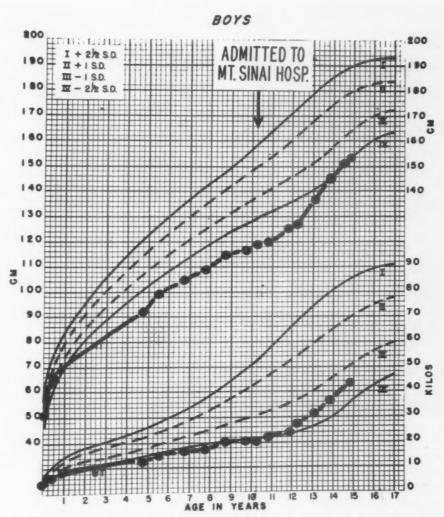


Fig. 1. Growth chart. Upper set of curves depicts 50th and 90th percentiles for height; lower set depicts similar ranges for weight. Note that patient's stature was below 90th percentile until age of fourteen years.

grams of the skull showed "extensive calcification of the falx cerebri and tentorium cerebelli." The child was then referred to The Mount Sinai Hospital.

On admission, the patient was found to be small in stature. (Fig. 1.) His cranial vault was quite large in relation to his face, thus producing a prominent forehead; otherwise his facies was unremarkable. Examination of the eyes revealed poor vision due to myopia, indistinct disc margins and thinning of the arterioles. Slit lamp studies of the cornea were negative. Bilateral pterygiums were noted. Some impairment of hearing was found. An apical systolic murmur was heard. The blood pressure was 120/85 mm. Hg. There were no other significant physical findings and neurological examination was completely within normal limits. The child was alert, bright and quite cooperative. There were no signs of cretinism.

Repeated examinations of the urine revealed the presence of pyuria and a trace to 1-plus albuminuria. The hemogram was normal, the hemoglobin varying

between 12 to 13 gm. per 100 ml. The erythrocyte sedimentation rate was 43 mm./hour; the blood glucose concentration, 95 mg./100 ml.; serum albumin level, 4.7 gm./100 ml.; serum globulin, 3.2 gm./ 100 ml.; and serum cholesterol, 350 mg./100 ml. Bone marrow examination was normal. An electrocardiogram demonstrated the presence of high T waves. Evaluation of kidney function included a blood urea nitrogen which varied between 46 to 75 mg./100 ml.; serum uric acid of 6.3 to 8.4 mg./100 ml., and serum creatinine level of 1.8 to 2.7 mg./100 ml. A concentration test showed inability to raise the specific gravity of the urine above 1.012. A phenolsulfonphthalein test resulted in the excretion of 13 per cent of the dye in fifteen minutes and a total of only 48 per cent was excreted after two hours. The urea clearance was 10.1 ml./minute (equivalent to approximately 20 per cent of normal). Urine culture revealed the presence of Escherichia coli. The initial serum calcium level was 15.8 mg./100 ml., phosphorus 4.4 mg./100 ml.;

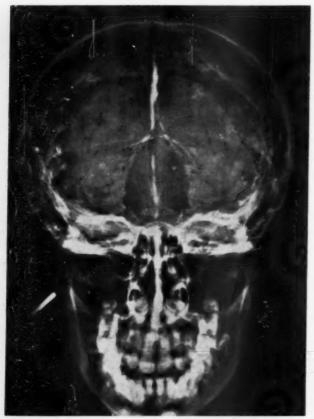


Fig. 2. Posteroanterior projection of the skull shows innumerable dural plaques in the tentorium, the falx and over both hemispheres. These are so extensive that the opening in the tentorium is completely outlined. The calvarium is thick but not sclerotic.

and alkaline phosphatase, 8 King-Armstrong units/ 100 ml. Two subsequent serum calcium levels were 13.4 and 14.8 mg./100 ml. After the patient had been given a Bauer-Aub low calcium diet for five days, 100 mg. of calcium was excreted in each of two twenty-four-hour urine specimens.

X-ray examinations of the abdomen, chest, skull, spine, long bones and pelvis were made during the hospital stay of the patient. X-ray film of the chest revealed no abnormalities. The abdomen showed the renal outlines to be within normal limits as to size, shape and position, but throughout the renal parenchyma on both sides there were multiple, punctate, calcific deposits characteristic of nephrocalcinosis. The skull showed moderate thickening of the calvarium in the frontal and parietal regions. The base of the skull did not appear to be remarkably osteosclerotic or thickened. The sella turcica was within normal limits. Throughout the dura, most obvious in the falx and the tentorium cerebelli, there were innumerable calcific plaques. (Fig. 2.) There was no definite evidence of calcification within the brain itself. The adenoidal soft tissue shadow was somewhat greater than would ordinarily be expected in a child of this age. The development of the teeth



Fig. 3. Several rather faint transverse bands of increased density are seen in the distal portions of the shafts of both tibias. These are rather poorly demarcated and located at some distance above the epiphyseal plates. The epiphyseal plates are irregular in outline. There may be cortical thickening over the lateral aspects of the fibulas. A short distance below the superior epiphyseal plate of the left tibia, on its lateral aspect, there is a small lucent zone with sharply sclerotic scalloped periphery which has the appearance of a cortical or Caffey defect.

appeared to be within normal limits although dental films showed evidence of pulp calcification. The lamina dura of the teeth were intact. The spine was normal except for the fact that the laminas of all of the sacral segments were absent and there was no evidence of centers of calcification of the coccyx. Examination of the legs (Fig. 3) showed multiple transverse bands of increased density in the lower portions of the shafts of both tibias which were rather poorly demarcated and were located 4 or 5 cm. above the epiphyseal plates. There was a suggestion that the cortex of the lateral aspects of the fibulas were somewhat thickened. The epiphyseal plates at the ankles and also at the knee joints were somewhat irregular in contour, but the density of the bone on either side of the plates appeared to be within normal limits. On



Fig. 4. The lower ends of the femurs show irregular intramedullary calcification characteristic of bone infarcts. The appearance of the epiphyseal plates is similar to those of the ankles.

the lateral aspect of the upper portion of the shaft of the left tibia, about 2 or 3 cm. below the epiphyseal plate, there was a sharply demarcated lucent zone with a sclerotic scalloped periphery which had the appearance of so-called cortical or Caffey defect. In the lower portions of the shafts of both femurs (Fig. 4) were areas of irregular dense calcific deposits which had the characteristic appearance of intramedullary bone infarcts. A similar but much smaller area was seen in the distal portion of the shaft of the right radius. There was marked bilateral retardation of growth of the carpal centers which particularly affected the navicular and the lesser and greater multangular bones and the distal ulnar epiphyses. There was similar marked retardation in growth of the centers for the trochlea, the medial epicondyle and the head of the radius bilaterally. Development of the bony centers appeared to be normal at the shoulder joints, the ankle joints and the knees. The delayed epiphyseal centers appeared to be those expected to appear at the age of four or five. There was no deformity of any of the bones.

The child underwent parathyroid exploration on June 17, 1954. Two parathyroids were removed; a third gland was seen and appeared to be normal on gross examination; the fourth gland was not found at surgery. Histological examination of the excised glands proved them to be normal. Postoperatively, the child suffered from hypocalcemia for twenty-four hours but recovered rapidly with appropriate therapy.

The patient has since been examined periodically in the Pediatric Growth and Development Clinic. He has remained in good health; he has progressed

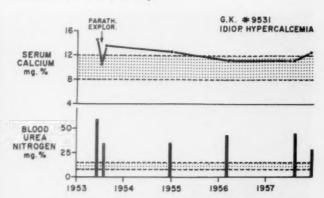


Fig. 5. Values for serum calcium and blood urea nitrogen observed over four-year period. Shaded areas refer to normal ranges.

through normal puberty and has undergone a remarkable adolescent growth spurt. (Fig. 1.) His general and facial appearance are normal. He has advanced through school, achieving superior grades. His blood urea nitrogen values remain elevated. The serum calcium levels have gradually fallen to normal (Fig. 5), in the absence of specific therapy and in spite of the fact that for approximately one year post-operatively the patient was given 1.5 gm. of calcium lactate daily. Roentgen examinations on three occasions have shown improvement in the appearance of the bones.

In December 1954, one and a half years after the original observations, the dural calcification, the nephrocalcinosis and the spina bifida of the sacrum appeared to be unchanged. Development of the lateral carpal centers and of the centers at both elbow joints was still moderately delayed but their appearance seemed somewhat more normal. Bone infarcts in the distal portions of the femurs were less marked and the cortical defect of the upper portion of the left tibia had disappeared. There was a remarkable increase in bone density of the epiphyses of the distal phalanges of the second and third toes of both the right and left foot. (Fig. 6A.) The epiphyses of the distal phalanges of the second and fifth digits of the right hand and the third, fourth and fifth digits of the left hand showed identical findings.

A third roentgen examination in February 1956, fourteen months after the second examination, showed a remarkable "catching up" of the growth of the epiphyses at the wrist and elbow joints. The bone age now appeared to be within normal limits at these sites. The abnormal density of the epiphyses of the distal phalanges of the toes was diminished and was confined to the central portions of these discs. (Fig. 6B.) The transverse zones of increased density at the lower ends of the tibias were absent and there was only slight residual intramedullary calcification in the lower portion of the left femur.

A fourth roentgen examination was carried out four years (July 1957) after the original observations. The



Fig. 6A. Examination of the toes of the right foot one and a half years after hospital admission shows marked increase in bone density of the epiphyses of the distal phalanges of the second and third digits. Identical findings were present on the opposite side and also in the similarly located epiphyses of the second and fifth digits of the right hand and the third, fourth and fifth digits of the left hand.

positive findings at this time were persistent nephrocalcinosis and dural calcification and persistence of the sacral laminar defects. The coccyx now appeared normal. There was a new finding, however,

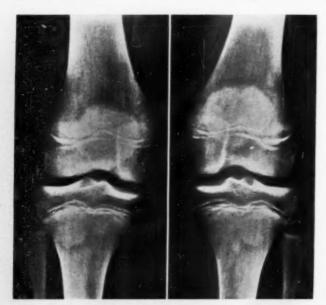


Fig. 7. Examination of the knees four years after the original work-up shows for the first time symmetrical, moderately well demarcated ovoid areas of increased bone density in the metaphyses of the upper ends of both tibias. These changes have been seen in renal osteodystrophy and are presumably unrelated to the original hypercalcemia.



Fig. 6B. Re-examination of the toes of the right foot fourteen months after the previous examination shows that the increased density of the epiphyseal plates of the terminal phalanges has diminished and is now confined to the central portions of these discs. Similar but less marked findings were present in the epiphyses of the distal ends of the humeri and the heads of the radiuses.

consisting of the presence of symmetrical rather spherical areas of increased density, moderately well demarcated, in the upper metaphyses of the tibial bones. (Fig. 7.) It is likely that these areas of bone sclerosis are not related to the hypercalcemia but perhaps represent changes of renal osteodystrophy [7].

A thorough investigation of the patient's status at fourteen years of age, performed simultaneously with the last roentgen evaluation described, revealed the following significant findings: His height was $59\frac{1}{2}$ inches and his weight was 84 pounds, both within the 90th percentile for his age. His blood pressure was 130/85 mm. Hg.

Examination of the eyes at this time demonstrated a myopic astigmatism correctible to 20/20 in each eye. Evaluation with the slit lamp showed bilateral symmetric opacification of the nasal and temporal portions of the paralimbal cornea. The opacifications consisted of granular and confluent areas of calcium located in the superficial areas of the cornea. They extended axialward approximately 3 mm. from the limbus. Blood vessels extended from the conjunctivas into the outer portions of the opacities, resembling pterygiums. (Fig. 8.) These findings, which apparently were developing during the preceding year, conform with the band keratopathy described as secondary to hypercalcemia per se [8]. Examination of the fundus revealed a small glial overgrowth on the left disc. Quantitative audiometric examination revealed a hearing loss in the left ear to the 30 decibel level for frequencies at and below 2,000 cycles for air conduction; in the right ear, a slight hearing loss to the 10

decibel level was present. Bone conduction was normal bilaterally. These findings were interpreted as secondary to previous infections which had affected the conductive mechanism of the middle ear.

The apical systolic murmur heard on initial examination was still present. Normal puberal changes in the scrotum and penis were present and the testes and pubic hair growth were of normal adolescent appearance. Evaluation of mental achievements revealed that the boy was of superior intelligence, with an I.Q. of 134 as measured by the Stanford-Binet test; his mental age was estimated to be eighteen and three-quarter years.

Laboratory data obtained during this evaluation included a normal hemogram and a normal urinalysis except for a trace of albumin. The erythrocyte sedimentation rate was 19 mm./hour. Blood examinations yielded the following results: blood urea nitrogen, 44 mg./100 ml.; serum sodium, 141 mEq./L.; uric acid, 8.0 mg./100 ml.; total serum protein, 8.6 gm./100 ml. with an albumin of 5.0 gm./100 ml. and a globulin of 3.2 gm./100 ml. Electrophoretic patterns of proteins and serum lipids revealed the following essentially normal results (normal values are within the parentheses):

Alpha-1 globul Alpha-2 globul Beta globulin	in. 55.0% (52.5%) in. 4.6% (4.2%) in. 10.9% (12.2%) 15.4% (14.0%) in. 14.1% (17.1%)
Cholesterol	
	230 mg./100 ml. (180 mg./100 ml.) 170 mg./100 ml.
Phospholipids.	260 mg./100 ml. (230 mg./100 ml.)
Lipoproteins	
Alpha	27% (35.3%)
Beta	$ \begin{array}{ccc} 47.2\% \\ 25.8\% \end{array} (64.7\%) $
O-lipoprotein	ns. 25.8% (64.7%)

The serum calcium was 11.2 mg./100 ml.; serum phosphorus, 3.7 mg./100 ml.; and alkaline phosphatase, 20.6 King-Armstrong units/100 ml. A Nickerson-Kveim test for sarcoidosis was negative.

In July 1957, at the conclusion of this evaluation, the patient was given a low calcium diet calculated to provide 225 mg. of calcium daily. Four months after institution of the diet, the results of his serum analyses were as follows: calcium, 12.5 mg./100 ml.; phosphorus, 3.0 mg./100 ml.; alkaline phosphatase, 21.0 King-Armstrong units/100 ml.; blood urea nitrogen, 28 mg./100 ml.; and total cholesterol, 224 mg./100 ml.

COMMENTS

Analysis of the twenty-five previously reported cases [9–25] of the severe type of idiopathic hypercalcemia reveals characteristics of this syndrome which are summarized in Table II.

The age of onset of symptoms is usually within

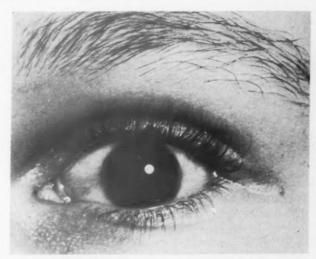


Fig. 8. Photograph of left eye demonstrating opacifications of the nasal and temporal portions of the paralimbal cornea. The right eye showed similar changes.

the first few months of life; the age of definitive diagnosis varied from five months to four and a half years, the usual time being at approximately eighteen months. There is no sex predominence. The principal presenting symptoms are failure to thrive, anorexia, vomiting, constipation and mental retardation. The chief physical findings are retarded height and weight, an apical systolic murmur, elevated blood pressure, a characteristic "elfin" facies and muscular hypotonia. The facies, which apparently is present in 60 per cent of the cases, has been described as consisting of prominent epicanthal folds, an overhanging upper lip, underdevelopment of the bridge of the nose and mandible and low-set ears [19]. Premature craniosynostosis and transient facial palsies are present in approximately 30 per cent of cases. Typical laboratory findings include hypercalcemia and axotemia in 100 per cent of the cases reported, accompanied in most instances by normophosphatemia and normophosphatasemia. Many of the patients have albuminuria and pyuria; somewhat less than half have an elevated serum cholesterol. The roentgen findings are characterized by increased bone density, amorphous in nature, in the flat bones, epiphyses and round bones; by sclerotic transverse bands at the ends of the shafts of the long bones; soft tissue calcification particularly in the kidneys (30 per cent of cases) but also in peripheral arteries in fascial planes, around large joints, in the dura, basal ganglia and bronchial tree; and by retarded bone age (50 per cent of cases). Occasionally, failure of tubulation of the long bones, cupping

Table II
IDIOPATHIC HYPERCALCEMIA—SUMMARY OF FINDINGS IN
TWENTY-FIVE REPORTED CASES OF SEVERE FORM

Characteristics	No. of Case	
Age of onset		
Under six months	22	
Age of diagnosis		
Under two years	18	
Sex		
Male	14	
Symptoms		
Failure to thrive	21	
Anorexia	21	
Vomiting	19	
Constipation	18	
Mental retardation	16	
Signs	10	
Small stature	23	
Cardiac murmur	18	
Elevated blood pressure	16	
"Elfin" facies	13	
Hypotonia	11	
Premature craniosynostosis	8	
Facial paralysis	6	
	11	
Elevated	11	
Roentgen involvement	25	
Long bones	25	
Skull	23	
Nephrocalcinosis	7	
Basal ganglia	3	
Soft tissues	2	
Bone age		
Retarded	7	
Normal	7	
Advance	1	
Not stated	11	
Prognosis		
Living, all findings persist	10	
Fatal	8	
Living, complete improvement	4	
Living, mental retardation only	2	
Not stated	1	

of the metaphyseal plates, bowing of long bones and premature craniosynostosis are seen. Bone infarcts such as were present in our patient have not been described previously and their pertinence, if any, to hypercalcemia is not evident. Resumption of normal bone formation leads to a rather characteristic appearance of the small bones since the originally excessively calcified central portions persist for some time.

The usual course of patients with severe form of this syndrome is persistence or progression of the physical findings, mental retardation and renal damage. One-third of the patients have died, usually within two years after the diagnosis has been established. These patients, together with ten other patients in whom the findings have persisted, make a total of 70 per cent with a fatal or poor prognosis. Only 4, or 16 per cent, are said to be living and "improved" during the rather short periods of follow-up.

The patient reported here apparently falls somewhere between the two forms of the syndrome. (Table 1.) His case is not an example of the usual form of the "benign variety" since the symptoms did not disappear within a few months after onset. There is kidney involvement and definite abnormalities are present in the bones as seen by x-ray examination. On the other hand, onset of symptoms was much milder than is usual in the "severe form," and ten years elapsed before measures to arrive at a definitive diagnosis were undertaken. The serious signs and symptoms of marked failure to thrive, constipation, "elfin" facies, hypotonia and mental retardation were lacking. Other manifestations such as the short stature, hypertension and systolic murmur, together with the characteristic biochemical findings, including an elevated serum cholesterol, and the roentgen findings correspond to the previously reported cases.

The chief difference, however, concerns the course. This child is the oldest known survivor. He is apparently undergoing normal adolescent development, including the characteristic growth spurt which has placed him finally within the 90th percentile for his age. (Fig. 1.) His mental attainments are superior. His biochemical and roentgen findings have apparently been stationary, at least for the four-year period during which he has been observed. For these reasons, this patient may be an example of a third or intermediate form of this syndrome.

This patient presented a puzzling diagnostic problem at the outset. None of the usual causes of an elevated serum calcium concentration could be incriminated. From the roentgen point of view, the findings did not conform to any of the conditions which cause an increased density of the bones [21]. Primary renal disease is not associated with elevated serum calcium. The child underwent parathyroid exploration to exclude remediable parathyroid tumor, with negative results. It was only in the course of four years of observation that the similarity of the findings in this patient with those reported in the original cases of idiopathic hypercalcemia was noted and the diagnosis suggested.

ETIOLOGY

Whether one accepts the various clinical forms as separate entities or as varying grades of severity of the same disease [26,27], it is difficult as yet to assign a definite etiology to the idiopathic hypercalcemia syndrome. Several possibilities have been suggested. Fanconi believed the syndrome to be due to an association of separate congenital defects [4]. Butler attributed the disease to an abnormal sensitivity to ingested calcium in the presence of primary renal disease [1]. Creery pointed out the high percentage of infants in his series who had received alkaline laxatives [9]. He compared the similarity of this condition to the "milk-alkali" syndrome in adults [28], and he suggested such medication as a causative factor. It does not appear that the syndrome is caused by primary parathyroid disease, by primary osseous pathology or by a primary renal disease. In addition to the lack of clinical support for these etiologies, autopsies have been performed upon several patients and findings consistent with any of these conditions are entirely absent. That the syndrome is the result of infection such as pyelitis or plasma cell pneumonia [29] in which hypercalcemia has been reported does not seem tenable.

At present, the opinion of those who have had the most experience with the syndrome favors vitamin D as the major etiological agent. It is obvious that vitamin D toxicity in the usual sense, i.e., administration of doses above 100,000 units daily for long periods of time, is not the cause since none of the reported patients have received vitamin dosage of this magnitude. Rather, it has been postulated that small excesses of the vitamin above the "usual" doses may be responsible. It has already been pointed out by Jeans that doses of vitamin D as small as 1,800 units per day may produce deleterious effects [30]. Studies of the order of magnitude of intake of vitamin D in Great Britain and Ireland have revealed that an appreciable number of infants in these countries may take as much as 4,000 units daily [31-33]. This is due to the fact that the National Dried Milk (the standard formula base) and the cereals have been heavily fortified with "extra vitamin." It is not as yet clear whether or not the continued use of these small excesses explains the greater incidence of the various forms of the hypercalcemia syndrome in Europe in contrast to the United States, where

smaller total daily vitamin D dosage is the rule. It is difficult to postulate a greater innate vitamin D hypersensitivity of European children as compared with American children. Furthermore, Hubble administered large doses of vitamin D to two children with the mild form of the syndrome in remission without producing a recurrence of untoward symptoms [34].

The clinical course, present status and lack of any unusual vitamin D intake in the patient reported here do not lend support to the vitamin D thesis. Rather the data in this case suggest a collection of separate congenital defects to be the cause of the syndrome, as was originally suggested. Another attractive hypothesis has been proposed by Forfar et al. and deserves consideration [35]. These authors suggest as the etiologic factor a disorder of cholesterol metabolism, leading to production of toxic sterols with excess vitamin D activity. The slightly elevated serum cholesterol, phospholipids and beta and O-lipoproteins found in our patient, and the similar findings in many of the other reported cases of both the mild and severe forms of the syndrome lend possible support to this theory. Perhaps idiopathic hypercalcemia can be explained as an inborn error of metabolism based on some enzyme defect in lipid and calcium metabolism.

THERAPY

Attempts at specific therapy of this syndrome have met with varying degrees of success. Removal of calcium and vitamin D from the diet have been tried. In the mild form, this approach has been successful in tiding the patient over to the point of spontaneous recovery. In the severe form, results with this form of treatment have been only moderately successful. The introduction of a decalcified milk may serve as an adjunct to this form of therapy [36]. Cortisone, used for the hypercalcemia of sarcoidosis [37], has been tried in idiopathic hypercalcemia, with moderate success [35]. The use of calciumbinding agents such as ethylenediaminetetracetate (EDTA) [11] and sodium phytate has been suggested [38]. The former is not without toxic effects; the latter has not yet been given an adequate clinical trial [24].

A low calcium, low vitamin D diet is being tried in the patient reported here. The hyper-calcemia and osseous changes are stationary at present and it may be that the disease can be classified as inactive. This regimen has been instituted with the hope of preventing progres-

sion of the undesirable sequelae of the syndrome, i.e., nephrocalcinosis and renal dysfunction.

SUMMARY

A fourteen year old boy, the oldest known survivor of cases of the severe form of idiopathic hypercalcemia, is reported.

Several important differences between the present patient and previously reported cases of the severe form of the syndrome are pointed out.

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Massive Metastatic Pulmonary Calcinosis in a Case of Multiple Myeloma*

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METASTATIC calcification has been defined as an alteration in calcium metabolism in which calcium salts are deposited in previously normal tissues [1]. This condition has been associated with a variety of diseases such as hyperparathyroidism, hypervitaminosis D, the milkalkali syndrome, extensive osteolytic lesions of bone such as seen in metastatic malignancy, and in multiple myeloma. It is the occurrence of massive metastatic calcification in the last named disease with which this communication is concerned.

CASE REPORT

E. G., a sixty-two year old widow, entered the Beth Israel Hospital in October 1956 complaining of pain in the back of several months' duration. On the basis of a characteristically abnormal serum electrophoretic pattern as well as marked replacement of bone marrow by plasma cells, a diagnosis of multiple myeloma was made. She was treated with x-ray, 1,250 r, to the lower spine, given a course of urethane, and discharged. Because of persistence of back pain she was readmitted on May 11, 1957. On physical examination the blood pressure was 210/100 mm. Hg, the pulse 84, and the temperature 100°F. Tenderness was marked in the left side of the chest cage posteriorly and anteriorly. The lungs were clear to percussion and auscultation. Heberden's nodes were noted and there was a question of minimal clubbing.

X-ray studies of the chest showed a pathological fracture of the left clavicle with diffuse osteoporosis of the rib cage. Skull roentgenograms showed the entire calvarium to be spotted with many small punched-out radiolucent areas. Urinalysis on admission showed 2-plus albuminuria. Hemoglobin was 10 gm. per 100 ml. and a white cell count was 4,100 per cu. mm. with a normal differential. The platelet count was 262,000 per cu. mm.

The patient received 10 mg. of meticorten four times a day. Albuminuria persisted. The urines were

negative for Bence Jones protein. Throughout hospitalization, examination of the lungs was negative to percussion and auscultation. A paralysis of her right leg and motor weakness of the left developed, with depressed touch and vibratory sensations bilaterally. The sensory deficit extended to the seventh dorsal vertebra. Reflexes became hypoactive. The neurological signs were interpreted as due to spinal cord compression from collapsed vertebrae. There were episodes of confusion, disorientation and aphasia. The sensorium cleared, the paresthesias of the legs and back pain persisted. The pain in the left shoulder was accompanied by crepitus and callus formation. The patient was discharged on June 18, 1957 to a hospital for chronic diseases for terminal

On admission to the Jewish Memorial Hospital the patient complained of pain in the posterior neck and inability to use her legs. The blood pressure was 220/108 mm. Hg, pulse 92. There was tenderness of the posterior neck and the rib cage. Tenderness, deformity and crepitus of the left clavicle were again noted. The lungs were clear to percussion and auscultation. Reflexes of the lower extremities were hypoactive.

X-ray studies of the chest taken on admission showed bilateral emphysema. A band of density at the right base consistent with a fibrotic strand or plate atalectasis was noted. The heart shadow was enlarged to the left and the aorta was widened and sclerotic. Films of the dorsal lumbar spine, sacrum, pelvis, hips, bones of the shoulder girdles, and ribs showed extensive osteolytic lesions, most marked in the seventh dorsal vertebra, the right superior pubic ramus, and the left descending ischial ramus. Pathologic fractures of both clavicles and a compression fracture of the seventh dorsal vertebra were noted. Urinalysis revealed 2-plus albuminuria and Bence Jones protein. The white cell count was 4,800 per cu. mm., hemoglobin 9.4 gm. per 100 ml., and hematocrit 31.5 per cent. Serum and urinary calcium levels were not determined.

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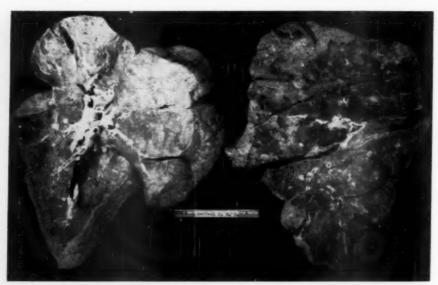


Fig. 1. Cut surface of both lungs showing peripheral distribution and lobular arrangement of the calcific process. Note that in the upper lobes these nodules extend well into the substance of the lung.

The hospital course was marked by progressive deterioration in the patient's condition. She became confused and disoriented. In July 1957 she sustained a fracture of the right clavicle while being moved. X-ray films showed an area of calcification adjacent to the right humerus consistent with peritendinitis calcarea. The red blood cell count remained around 2,400,000 per cu. mm. and the hemoglobin was 7.0 gm. per 100 ml. The white cell count ranged between 4,500 and 7,300 per cu. mm., and on one occasion two plasma cells were seen in a peripheral blood smear. On August 13 the pulse was 110 and moist rales were noted in both posterior basal lung fields. X-ray of the chest showed generalized increase in coarse markings throughout both lungs, interpreted as consistent with congestive heart failure. She was treated with digitalis and given diuretics. The patient failed rapidly and died sixty-two days after admission.

Autopsy findings* were as follows: The body was that of an obese white woman. There was no adenopathy or peripheral edema. The sternum was removed; it was so fragile that it was easily broken. The heart weighed 395 gm. The left ventricular muscle was hypertrophied but there was no evidence of cor pulmonale. The myocardium showed no areas of calcification or scarring. The coronary arteries exhibited minimal atheromatous change and no thrombi.

Both lungs filled their respective cavities. There were no pleural adhesions on either side. About 100 cc. of clear straw-colored fluid was found in the left pleural cavity, and 50 cc. in the right. The overlying pleural surfaces were smooth and glistening, and there was minimal anthracotic pigmentation. The left lung weighed 470 gm., the right 550, and each had the

normal number of lobes. On examination of the uncut lungs many flat, raised, plaque-like areas were noted on the surfaces of all lobes. These areas felt hard and nodular, and were noted to extend well into the substance of the lung. The diameters of each of these nodular areas varied from 2 to 3 up to 8 or 9 cm. On cutting into the substance of the lung one noted a marked resistance to the knife as well as a definite feeling of grittiness. On the cut surface of the upper lobe of the left lung these nodular masses appeared whitish brown and lobular. They were distributed around the peripheral areas of the lobe, with a large wedge-shaped area of calcification in the lingula. The lower lobe of the left lung had less extensive peripheral calcification than the upper lobe.

In the right lung the peripheral distribution of these nodular masses was also noted. A large wedge-shaped area of calcification and consolidation occupied the medial aspect of the upper lobe as well as the basal segment of the lower lobe. In some areas these lobules were coalesced into large hard masses measuring up to 10 centimeters in depth. (Fig. 1.) On closer examination it appeared that the cut edges, instead of retracting, remained straight and sharp. The cut surface of these nodular masses had a porous, honeycombed appearance, much the same as a bath sponge. (Fig. 2.) The remaining lung tissue was light red and markedly edematous; a frothy pink fluid was easily expressed when pressure was applied. The vasculature of both lungs was exposed and many emboli were seen occluding the larger branches of the pulmonary artery. The emboli were firm and fixed to the arterial walls and not easily removed. Emboli were seen occluding the large arteries leading to the large wedge-shaped areas of calcification and consolidation of the upper and lower lobes of the right lung and both lobes of the left lung. Emboli were also found occluding many of the

^{*} Autopsy performed by Dr. M. Magruder and Mr. W. B. Goldfarb.

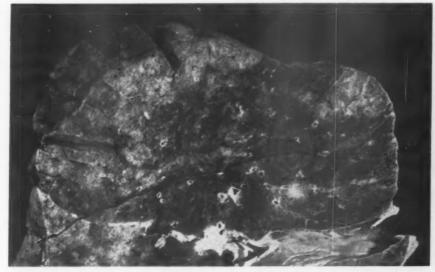


Fig. 2. Close-up of cut surface of upper lobe of left lung showing lobular arrangement of the calcified regions as well as the porous, honeycombed appearance of these areas. Note the lack of retraction of the cut surface. A pulmonary embolus is also seen.

smaller branches of the pulmonary arterial tree. The bronchial tree was found to contain a thick tenacious mucus; however there was no occlusion of the bronchi.

Each kidney weighed 220 gm. and both were large, smooth, soft and pale. On cut surface small yellowish white firm stones were noted around the renal papillae filling the pelves. The pelvic mucosa showed scarring and fibrosis. There were no stones in the ureters. The bladder was found to contain a yellow-white viscid material with many small concretions similar to those in the renal pelves. The bladder mucosa was hemorrhagic and edematous. The stomach showed an absence of rugal folds and atrophy of the mucosa. There was no gross evidence of calcification of the stomach. The fourth through the ninth ribs on the left side were fractured, as were the bodies of several thoracic vertebrae. The ribs were soft and easily broken. The vertebral bodies were misshapen and had irregular buigings of soft tissue masses along their surfaces. On cut surface these nodular areas were seen to be composed of soft pale red marrow which was easily scraped away with a knife. The parathyroid glands were not examined and the source of the pulmonary emboli was not determined.

On microscopic examination of the lungs the most striking feature was the marked calcification of the alveolar walls. In many areas the calcium seemed to replace the walls as thick irregular masses, whereas in other fields the calcification was minimal and represented by fine granular deposits seen best at high power. On hematoxylin and eosin stain the calcium was also seen to impregnate and coat the elastica of the pulmonary parenchyma. Sections from the central areas of the lung which were not grossly involved in the calcific process showed a marked decrease to complete absence of calcification of the alveolar walls. In

the calcified regions an epithelial proliferation within the alveoli was readily apparent, and there was also evidence of an increase in the amount of collagen in the lung in these areas. In many areas the alveolar spaces were obliterated by the overgrowth of a fine granulation tissue. In some sections a resorptive pneumonitis characterized by a histiocytic response was present while other alveoli showed evidence of recent hemorrhage. Several foci of fresh purulent exudate were scattered throughout both lungs. The walls of many bronchioles, smaller bronchi and alveolar ducts showed calcific deposits. The deposition was mostly subepithelial in location; however in several fields it was seen to involve the basement membranes and extend into the adjacent connective tissue. The cartilage of some of the larger bronchi was also involved in this process. The blood vessels showed calcification in varying degrees, from the presence of a few granules in the media to complete replacement of the walls by large calcified plaques. In some of the arteries this calcification on cross section appeared as a complete ring of basophilic material replacing the media. This was accompanied by a thickening and edema of the intima with an over-all decrease in the size of the vessel lumen. An obliterative endarteritis characterized by the presence of old organized pulmonary thrombi or emboli, many of which were impregnated with calcium, was also noted. In some of the larger vessels the calcific deposits were irregular and wavy in appearance, suggesting impregnation of the internal elastic lamina. In many instances a continuity of the calcium deposits in the walls of arteries with those of alveolar capillaries was noted. (Fig. 3.)

Decalcified sections of the lung showed a thick hyalin-like material with the brilliant staining quali-

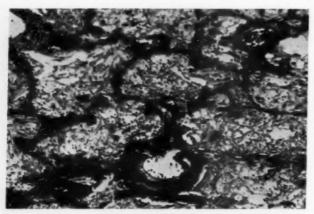


Fig. 3. Microscopic section of the calcified portion of the lung showing the extensive involvement of the alveolar walls by this process. The wall of a small artery is seen to be almost completely calcified. A fibroblastic overgrowth of the alveolar spaces is well illustrated here.

ties of osteoid in all places where the calcium was deposited, such as the alveolar walls, beneath the bronchial epithelium, and in and around blood vessel walls. Sections of lung stained for the presence of amyloid by the Congo red method and by cresyl violet were within normal limits. The Prussian blue reaction for the presence of iron was also negative. Verhoeff's elastic tissue stain of sections of the lung periphery showed a marked increase in the elastic fibers in the pulmonary parenchyma. This was largely responsible for the thickened alveolar walls and formed the basis for the calcific deposits. The elastica of the small arteries was also thickened and coarsened in appearance. Mallory's connective-tissue stain showed an increase in the number and thickness of collagen fibers in many of the alveolar walls and blood vessels. These areas corresponded to the hyalin-like tissue seen in sections of the decalcified preparation stained with hematoxylin-cosin. This picture of pulmonary elastosis and increase in collagen with superimposed calcification was complicated by a hyperplasia of the alveolar duct epithelium which in many instances epithelialized the alveoli.

The heart showed minimal subendocardial fibrosis and several scattered foci of calcification within the myocardium. Fatty infiltration with lobular atrophy and interstitial fibrosis of the pancreas were present. There was also calcification of the walls of some of the smaller arteries. The spleen showed evidence of myeloid metaplasia as well as plasma cell infiltration. Minimal myeloid metaplasia and periportal fat deposition were noted in the liver. The stomach showed mucosal atrophy with no evidence of calcification. The remainder of the gastrointestinal tract was normal. Sections of the kidneys showed foci of calcification in glomerular tufts, arteriolar walls, and in some of the collecting tubule epithelial cells and lumina. There was marked interstitial fibrosis with atrophy and lipoid degeneration of many of the renal tubules.

Bence Jones protein casts with giant cell reaction were present. Changes of chronic cystitis and calcific encrustation of the bladder mucosa were also present. The bone marrow was replaced by clusters of closely packed, oval, eccentrically nucleated myeloma cells. Here and there were noted foci of erythropoiesis and developing leukocytes. A hyalin-appearing brilliant eosinophilic material, similar to that found in the decalcified sections of lung, was seen to course irregularly through the tumor and to impregnate blood vessel walls.

COMMENTS

A review of the literature reveals that most descriptions of metastatic calcification of the lungs in multiple myeloma have been sparse and incomplete. An anatomical feature worthy of consideration here is the peculiar distribution of the calcium around the periphery of all lobes in a coalescent but distinctly lobular pattern. The relationship between this peripheral lobular distribution to the presence of multiple organized pulmonary emboli will be considered. It should also be pointed out that despite the marked involvement of the lungs there was no apparent evidence of this process on radiologic examination. This may be explained by the fact that no atelectasis or solid nodularity was present. The alveoli retained their shape and were aerated despite the fact that their walls were calcified and rigid.

Several factors are involved in the production of metastatic calcification. Mulligan [1], in an extensive review of the subject, places particular emphasis on the importance of local soft tissue alkalinity caused by a high blood oxygen or low carbon dioxide content, such as occurs in the alveolar capillaries, pulmonary veins, left side of the heart, and the systemic arteries. He also reemphasizes a long-held theory [2-4] of metastatic calcification, that those tissues which excrete acid products are thereby rendered temporarily alkaline and so favor the deposition of calcium salts. Thus the gastric mucosa secreting hydrochloric acid; the kidneys, acid phosphates; and the lungs, carbon dioxide are mentioned as the most common sites involved in metastatic calcification. In his series of metastatic calcification the lungs and kidneys were involved in 65 per cent of the cases, the heart and arteries in 43 per cent, and the gastric mucosa in 25 per cent.

Another important factor in the mechanism of metastatic calcification is the level of calcium in the blood. Although no quantitative correlation has been made, the conditions in which meta-

static calcification has been described are characterized by hypercalcemia. The occurrence of hypercalcemia in multiple myeloma was first described more than twenty years after the first descriptions of soft tissue calcification in this disease [5]. Reports [6-10] have since appeared regarding the incidence of hypercalcemia in multiple myeloma; however none has mentioned the relationship between the blood calcium level and the extent of soft tissue calcification. Albright and Reifenstein [11] and others [12] attribute the rise in blood calcium level in multiple mycloma to the fact that the lesions dissolve bone salts into the blood stream more rapidly then the kidney can clear the blood of excess calcium. Associated with this is a tendency to renal calcification, the decrease in renal function causing a secondary increase in parathyroid activity which tends to perpetuate and increase the hypercalcemia and metastatic calcification. Lichtenstein and Jaffe [13] also note that the hypercalcemia may be accentuated by secondary parathyroid hyperplasia in response to chronic renal insufficiency from such causes as the precipitation of Bence Jones protein or the presence of calcification of the renal tubules. However, in their series of thirty-five cases none showed any evidence of parathyroid hyperplasia at postmortem. Wainwright [14] proposes that the renal failure which often occurs in the hypercalcemic states results in a metabolic acidosis which is compensated for by the excretion of additional carbon dioxide from the lungs by hyperventilation; the rise in pH of the blood in the lung capillaries may, in turn, explain the fact that calcification in the lung is usually very extensive and more marked than in any other organ. This is also consistent with the theory of tissue alkalinity as the important local factor in the mechanism of this process.

In this case it was noted that in all lobes there were multiple pulmonary emboli occluding the branches of the pulmonary arterial tree. The distribution of the calcification was lobular and peripheral, similar to the anatomical pattern seen in multiple pulmonary infarcts, whereas the central regions were free of calcium. However, there were no infarcts in these lungs. Also noted was the fact that the emboli were organized and many were calcified, thus giving evidence that this was not a terminal process. One may postulate, on the basis of these observations, another mechanism in the production of this massive calcification. Since there were multiple pulmo-

nary emboli, there was less flow of blood to the lungs, especially to the peripheral regions. This decreased pulmonary arterial flow could have produced a relative alkalinity in those regions because there was less blood with carbon dioxide to excrete and therefore this may have altered the calcium salt solubility and thus favored local tissue calcium deposition. The fact that there was no gastric mucosal calcification and that the renal depositions were minimal, in the presence of the massive pulmonary calcification, indicates that the local pulmonary vascular factor must have been an important factor in the pathogenesis of this lesion.

It is difficult if not impossible in this case to determine whether the pulmonary embolization preceded or followed the development of the massive metastatic calcification of the lung parenchyma. This point is of some importance for if the pulmonary emboli did precede the calcification, and if we accept the concept of metastatic calcification as having occurred in previously normal tissues, this is not truly a case of metastatic calcinosis but one of a dystrophic nature. However, the clinical history does not indicate the time when the emboli occurred, nor is there evidence of cor pulmonale, so that one may conclude that this is indeed a case of metastatic calcinosis with a superimposed dystrophic component manifested by the multiple pulmonary emboli.

SUMMARY

The clinical history and a detailed description of the pathologic anatomy of the lungs of a sixty-two year old woman with metastatic pulmonary calcinosis secondary to multiple myeloma is presented.

The mechanisms involved are discussed.

Acknowledgment: I wish to express my appreciation to Dr. Joseph Giammalvo who has given me so much help in the preparation of this paper. I also wish to thank Dr. H. Baker, physician in chief at the Jewish Memorial Hospital, for his permission to use the clinical material for this case.

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Fatal Chylopericardium Caused by Hamartomatous Lymphangiomatosis*

Case Report and Review of the Literature

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ONLY three cases of primary chylopericardium have been reported in the literature to our knowledge [1–3]. All three patients were subjected to prolonged investigation, and two were treated for tuberculous pericarditis, before the correct diagnosis was established. Definitive treatment consisted of ligation of the thoracic duct low in the right posterior mediastinum. In two cases no cause for the chylous effusion was found at surgery; in the third [1] a superior mediastinal hygroma (lymphangiomatous hamartoma) was present. In all cases recovery was uneventful, and all three patients were well six months to two years after the operation.

The case to be described is the first instance to our knowledge of hemorrhagic chylopericardium caused by a lymphangiomatous hamartoma. It illustrates the diagnostic problems posed by chylopericardium, the clinical course characterized by progressive cardiac and pulmonary insufficiency, and the need for correct and early surgical intervention.

CASE REPORT

C. M.,‡ a fifteen year old English-born white schoolgirl, was first admitted to the University of California Medical Center, San Francisco, on April 4, 1957, because of dyspnea and orthopnea of one month's duration. Her birth and early development had been normal. When she was five years old a dry cough and episodes of "asthmatic" wheezing had developed which occurred intermittently since that time. No abnormality had been noted in a routine x-ray examination of the chest taken when she was eight years old. A second film at thirteen years of age

‡ Studied through the courtesy of Dr. William A. Atchley.

showed generalized cardiac enlargement and pleural thickening. (Fig. 1.) One month later she had mild exertional dyspnea, a sharp catching pain in the lower right side of the thorax, and hemorrhages from the subconjunctiva and soft palate, but no hemoptysis. These symptoms steadily increased in severity, and the patient became weak and extremely emaciated. Further past history and family history were not contributory. Injury to the chest and falls were denied. There was no known exposure to tuberculosis.

The patient, an alert frail girl who appeared chronically ill, was mildly dyspneic at rest. Temperature was 37.5°c. Respirations were shallow at 28 per minute. Heart rate was 100, with a paradoxical pulse. Blood pressure was 110/80 mm. Hg. The lips and nails were slightly cyanotic. Small bilateral axillary nodes were palpated. A resolving subconjunctival hemorrhage and petechiae were noted on the soft palate and both tympanic membranes. Neck veins were distended when the patient was in the sitting position (venous pressure, 365 mm. water). The anterior-posterior diameter of the chest was increased; there was a slight precordial bulge. Breath sounds were diminished, and scattered expiratory wheezes were heard. The heart sounds were muffled; no murmurs were heard. The apical impulse was not palpable, and dullness extended from 3 cm. to the right of the midline to the left mid-axillary line. The liver edge extended 5 cm. below the right costal margin; the spleen was not palpable. Neither ascites nor edema was present.

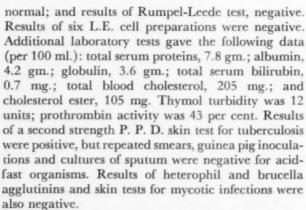
Results of routine laboratory studies were as follows: urine, normal; hemoglobin, 10.4 gm. per 100 ml.; hematocrit, 35 per cent; red blood cells, 4,000,000 per cu. mm.; sedimentation rate (Wintrobe), 5 mm.; cell indices, normal; white blood count, 3,650 cells per cu. mm., with 56 per cent neutrophils, 29 per cent lymphocytes, 4 per cent basophils, and 10 per cent monocytes; platelets, 90,000 per cu. mm.; bleeding and coagulation time,

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Ftg. 1. Generalized cardiac enlargement and pleural thickening in film taken when patient was thirteen years old, two years before hospitalization.



An electrocardiogram showed ST depression with a low T in leads II, III, and AVF and general low voltage. A chest film showed generalized pleural thickening and slight, diffuse pulmonary infiltration (more prominent in the right lung). The heart size had increased since the film taken two years previously. (Fig. 1.) Fluoroscopy disclosed diminished cardiac pulsation. Vital capacity was 0.75 L., pulmonary function studies were normal except for severe arterial oxygen desaturation. Serum electrolytes were compatible with mild respiratory acidosis.

Biopsy of a left axillary node on April 8 showed non-specific lymphadenitis and histiocytic hyperplasia, but no evidence of malignancy. A sternal marrow smear was normal, except for mild monocytosis.

The patient remained afebrile, but was dyspneic at rest and complained of precordial tightness. Occasional episodes of wheezing were relieved by aminophyllin suppositories. On April 13 thoracentesis was attempted at multiple sites. Fluid was obtained only at the left posterior axillary line in the eighth intercostal



Fig. 2. Pneumopericardiogram taken May 10, immediately after aspiration of 1,500 ml. of fluid and injection of 150 ml. of air. Note air-fluid level within thickened and enlarged pericardium.

space. Removal of 500 ml. of dark sanguineous fluid resulted in immediate relief of the dyspnea, chest pain and paradoxical pulse, indicating that the fluid had been drained from the pericardial sac. A diagnostic paraxyphoid pericardial aspiration on April 16 yielded 120 ml. of similar fluid. No acid-fast organisms or malignant cells were found in smears of the fluid.

A working diagnosis of tuberculous pericarditis was made, and a regimen of therapeutic doses of isoniazid, streptomycin and dihydrostreptomycin, plus vitamin K₁ oxide, ferrous sulfate and vitamin supplements, was instituted.

On April 24 a diagnostic biopsy of the pleura and right lung showed non-specific fibrosis, but no evidence of tumor. Cultures of the tissue were negative for both pyogenic organisms and tubercle bacilli. On April 29 digitalis and diuretics were instituted because of progressive orthopnea and dyspnea. Recurrent tamponade necessitated another aspiration of 1,500 ml. of dark sanguineous fluid on May 10, following which approximately 150 ml. of air was injected into the pericardial sac. X-ray films taken immediately thereafter revealed an air-fluid level within a thickened and enlarged pericardium. (Fig. 2.) The heart appeared normal in size. Severe postural hypotension was present for several days after the air injection. The possibility of hemorrhagic serositis prompted the addition of prednisone, 30 mg. daily, to the patient's regimen at this time.

Because of recurrent pericardial tamponade, 700 ml. of fluid was again aspirated on May 14, 1,000 ml. on May 18, and 700 ml. on May 21. In all instances the fluid was grossly bloody and did not clot on standing; the specific gravity was 1.025, the

hematocrit was constant at 10 per cent. Repeated L.E. preparations of the fluid, smears for malignant cells and studies for pyogenic organisms, acid-fast bacilli, and fungi were negative. It was noted that after several days of refrigeration the fluid separated into four distinct layers; a red cell layer containing numerous crenated cells in distinct rouleau formation, a buffy layer containing mature neutrophils and lymphocytes and many mesothelial-like cells, a yellow colloidal layer, and a milky surface layer which contained no cells. As a screening test for fat, the milky layer was extracted with ether and stained with Sudan III. Large numbers of sudanophilic droplets were seen in the residue, suggesting the anomalous presence of chyle in the pericardial sac.

Analysis of specimens of pericardial fluid obtained under fasting conditions showed the following (per 100 ml.): total protein, 4.9 gm.; albumin, 2.7 gm.; globulin, 2.2 gm.; total lipid, 690 mg.; and cholesterol, 103 mg. Blood taken simultaneously contained 480 mg. of total lipid and 140 mg. of cholesterol per 100 ml. Lipids separated from the fluid by ultracentrifugation were composed of 83 per cent triglycerides and 1 per cent protein. This lipid pattern is the same as that determined by Havel et al. [4,5] for chylomicrons. These results eliminated the possibility that the milky layer contained "pseudochyle" and confirmed the hypothesis that the fat in the pericardial fluid was of chylous origin.

On May 25, immediately after a pericardial aspiration, the patient was fed 50 mg. of Sudan III dissolved in 100 ml. of warmed safflower oil and 200 ml. of cream. Six hours later fluid was again aspirated, extracted with ether and dried. The residual film was grossly pink and contained fat globules stained with Sudan III.

Sixty days after admission, it was apparent that the patient's condition was gradually deteriorating despite antituberculous and steroid therapy and repeated pericardial aspirations. Thoracotomy was then scheduled. During the ensuing three weeks while she was being prepared for the operation, the patient required four pericardial aspirations (totaling 2,450 ml. of fluid).

On June 25, five hours after the patient had eaten a fatty meal, left thoracotmy was performed by Drs. Gordon Sproul and Brian Stringer. The chest cavity, which was entered through the seventh left intercostal space, contained several hundred ml. of chylosanguineous fluid. The pericardium was grossly edematous; its surface exuded bloody chyle when nicked. The pericardial fat was discolored and spongy, and oozed chylosanguineous fluid. Six hundred ml. of similar fluid was removed from the pericardial sac, which was remarkably thin and flexible compared to its appearance in the preoperative pneumopericardiogram. The visibly rapid accumulation of fluid in the sac was striking: in ten minutes some 50 ml. appeared; after its removal the same amount reaccumulated in a similar time. The fluid appeared to flow from many

areas within the pericardium. Since the source of fluid could not be localized, the mediastinal pleura was entered just above the diaphragm. Many large, branching lymphatics were found. Attempted cannulation of one of the larger channels was unsuccessful. Further dissection around the esophagus and base of the pericardium disclosed numerous dilated lymphatics, 2 to 9 mm. in diameter; these were ligated. After closure of the mediastinum, a larger pericardial window was fashioned.

No evidence of neoplasm involving the heart or pericardium was found. The lung, which appeared to have a filmy coating of fibrin, was somewhat restricted in expansion. Because of the patient's debilitation the lung was not decorticated. Before the chest was closed two thorostomy tubes were placed in the region of the pleuropericardial window. There was no accumulation of fluid in the pericardial cavity at this time.

The immediate postoperative course was uneventful, and the drains were removed on the third day. Because of increasing dyspnea and signs of left pleural effusion a thorostomy tube was inserted on the tenth day. Approximately 500 ml. of fluid drained daily for one week; during this week the patient was free of symptoms. Thereafter, as the drainage diminished and finally ceased, the patient's dyspnea gradually returned. The thorostomy tube was removed on the twenty-eighth day. By the forty-first postoperative day the patient had severe symptoms of tamponade which were relieved by pericardial aspiration of 600 ml. of chylosanguineous fluid. It became apparent that closure of the pleuropericardial window and recurrence of pericardial effusion were responsible for the simultaneous decrease in drainage and increase in symptoms. Four additional pericardial aspirations (3,300 ml. of fluid) were required during the next week. On the forty-seventh day, after removal of 1,200 ml. of fluid from the pericardial sac, the patient went into shock. She died twelve hours later, on August 12, 1957.

At autopsy the most striking features were the extreme emaciation and the findings in the chest cavity. The pleural spaces were completely obliterated by dense fibrous tissue which surrounded the lungs and mediastinal organs. The scar tissue was interlaced by many widely dilated lymphatic channels. These tortuous vessels formed a morass of such complexity that it was impossible to find a single point of entry into the pericardial space. Fibrosis was so extensive that only sharp dissection could free the intrathoracic organs. Microscopically, the scar tissue was composed of collagenous fibers, heavily infiltrated with chronic inflammatory cells. The interlacing lymphatics were composed of smooth muscle, fibrous tissue and endothelial lining cells. These vessels communicated directly with the lymphatics of the interlobular spaces of the lungs, which in turn appeared to be in continuity with the perivascular lymphatics of the pulmonary parenchyma. On gross examination the lungs

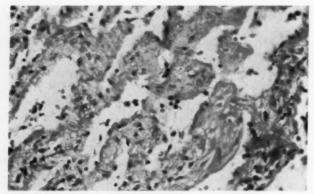


Fig. 3. Thickened pleura containing many dilated lymphatic spaces.

were extremely fibrous and firm in consistency. Microscopic examination showed fibrosis of the pulmonary alveolar septums and dilated perivascular lymphatics. (Fig. 3.) The pericardium, which was also fibrotic, measured 22 mm. in thickness. (Fig. 4.) Microscopically it was composed of dense collagenous tissue infiltrated by chronic inflammatory cells and numerous dilated lymphatic spaces, many of which contained fresh red blood cells. (Fig. 5.) Gross examination of the heart showed right ventricular hypertrophy and dilatation; microscopically, the perivascular lymphatics within the myocardium were also dilated. The thoracic duct was identified at its point of entry into the left subclavian and left internal jugular veins, and was normal in this area. The duct could not be traced downward; it immediately became lost in the great profusion of lymphatic channels in the mediastinum. Directly above the diaphragm and subjacent to the azygos vein, which measured 9 mm. in circumference, was a single lymphatic channel 14 mm. in circumference. (Fig. 6.) This channel disappeared into the dense scar tissue at a point 2 cm. above the diaphragm. The abdominal organs appeared normal. The cisterna chyli, in contrast to the multiple channels above the diaphragm, was a single, slightly dilated duct. The lymph nodes surrounding it were slightly enlarged, and micro-

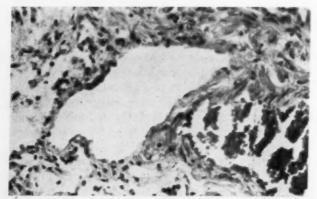


Fig. 5. Pulmonary parenchyma showing dilated lymphatic channel.



Fig. 4. Incised thickened pericardium at autopsy.

scopically showed extramedullary hematopoiesis and some dilatation of the hilar spaces.

The diagnosis was hamartomatous lymphangiomatosis of mediastinum with lymphangiectasia of lungs, pleura, pericardium and heart.

COMMENTS

A localized lymphangiomatous hamartoma was the underlying cause of the chylopericardium described by Groves and Effler [1]. In our patient a far more extensive hamartoma involving all the intrathoracic lymphatics was found at autopsy. The fact that the lymph channels were so numerous and so well differentiated points toward a congenital defect [6,7].

The following hypothesis might explain the clinical course and findings at autopsy. The patient remained asymptomatic until rupture of one or more of the abnormal lymphatic vessels resulted in spillage of chyle into the thoracic cavity. The response to the irritant effect of chyle was mediastinal and perilymphatic fibrosis, which in turn caused partial blocking of lymphatic flow. The resultant increase in lymphatic pressure may have allowed further leak-

age of chyle into the surrounding tissues, thereby intensifying the inflammatory reaction. The effect of chyle on tissue was demonstrated by the thickened and distorted appearance of the pericardium and pleura at autopsy compared to their relatively normal appearance at the time of thoracotomy. The presence of blood in the chylous effusion apparently was caused by rupture of the thin-walled lymphatic and blood vessels into one another, as evidenced by the multiple venolymphatic aneurysms seen in the postmortem histologic sections.

Creating the pleuropericardial window undoubtedly aggravated the inflammatory process in our patient. Meade [8], in discussing the management of chylothorax, has emphasized the hazard of permitting irritating chyle to remain in the thorax. In our patient earlier ligation of the lymphatic channels might have obviated the need for a pericardial window and prevented much of the pulmonary, pleural and pericardial fibrosis which contributed to her death. Naef [2] advocated early surgical intervention in chylopericardium and recommended right thoracotomy as the preferred approach. In massive chylothorax, cures have been achieved only by ligation of the thoracic duct [9-13], which is almost always found in the right posterior mediastinum [14,15]. In our case a thoracotomy on the right probably would have been more successful and would have provided a better opportunity to ligate the multiple lymphatic channels. Interruption of the thoracic duct below the diaphragm, where it was a single channel, might also have succeeded in diverting the flow of chyle away from the distended thoracic lymphatics.

The difficulties in the diagnosis of chylopericardium and the importance of diagnostic tests are also emphasized by our findings. In the three cases previously reported in the literature [1-3], the diagnosis was first suggested by the cloudy or milky nature of the pericardial fluid. This was also true in our patient, although initially the blood in the fluid obscured its milky character. The appearance of an orally administered lipotrophic dye (Sudan III) in the pericardial fluid was useful in forming the diagnosis in our patient, as well as in two of the previous patients [1,3]. Here again, the presence of blood in the pericardial fluid of our patient made it difficult to recognize the orange-stained fat droplets. The dark green dye, D and C Green No. 6, which Klesper and Berry have



Fig. 6. Cannulated dilated lymphatic channel adjacent to azygos vein.

recommended [16], would probably be more easily detected when bloody effusions are concerned. The chemical studies of chylomicrons obtained by ultracentrifugation were helpful in substantiating the diagnosis.

SUMMARY

This report describes a fatal case of chylopericardium associated with an extensive hamartoma of the intrathoracic lymphatic channels. The diagnosis was finally established by determining the lipid composition of the hemorrhagic chylous effusion and by the use of an orally administered lipotrophic dye. Left thoracotomy and ligation of many of the mediastinal lymphatics was unsuccessful in relieving tamponade, and cardiorespiratory insufficiency led to death. Postmortem findings revealed a congenital defect of the intrathoracic lymph vessels leading to extensive lymphangiomatosis and lymphangiectasia.

Acknowledgment: We wish to express our appreciation to Drs. Philip Strauss, Richard

Porter, John Farquhar and Richard Havel for invaluable assistance in the clinical management and laboratory evaluation of the case, and to Dr. Jackson Crane for his assistance in the interpretation of pathologic findings.

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Sudden Coma Induced by Mumps Virus*

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I be eliminated from the differential diagnosis, the organic diseases most likely to be considered first in the comatose patient are intracranial bleeding, intracranial neoplasms and infection. The production of coma during the course of bacterial infections of the central nervous system is well known but the possibility of sudden coma induced by a virus is not usually considered.

Many viruses encountered in this country may cause meningoencephalitis but overt coma as a feature of such infections is usually absent, particularly since arthropod-borne viruses such as St. Louis and equine encephalitis have been repressed by mosquito control. Coma with Coxsackie, ECHO, poliomyelitis and lymphocytic choriomeningitis viruses is rare and, in fact, has not been reported with the former two. Coma has been reported, of course, with poliomyelitis but always in association with muscle weakness, paralysis or severe respiratory distress, thus suggesting the diagnosis.

Mumps infections constitute one of the most frequent causes of viral meningoencephalitis ranging from 10 to 40 per cent of all cases of mumps, depending upon the criteria used for establishing such a diagnosis. It is well known that mumps meningoencephalitis may occur without a preceding parotitis but the fact that mumps virus may cause sudden unconsciousness with few prodromata has not been documented. The present report describes two such cases in which the admission findings suggested intracranial tumor or encephalitis of unknown etiology and in which subsequent viral studies showed the etiologic agent to be mumps virus.

CASE REPORTS

CASE I. T. D., a seventeen year old Negro schoolboy, was brought to Duke Hospital because of coma of approximately twelve hours' duration. The brief history was obtained from the family who stated that the patient had been entirely well until the morning of admission when he was found in bed groaning and unresponsive to his surroundings. Further questioning revealed that for the two days prior to admission he had complained mildly of headache and sore neck; however, the patient had had frequent headaches for the past several years and the present symptoms apparently were disregarded both by the patient and by his parents. The past history was non-contributory. He was said to have had all the usual childhood diseases, including mumps.

On examination the blood pressure was 124/ 52 mm. Hg, pulse 56, respirations 20, and temperature 38.7°c. (Fig. 1.) He was a well developed, slender boy, semicomatose and unresponsive to the examiner. Usually he lay still but occasionally writhed or groaned. He did not respond to any stimulus including deep pain, but the tendon reflexes were present although they were definitely hypoactive. The eyes were tightly closed and resisted opening, but when opened were thought to deviate to the right. The parotid glands were not enlarged. Respirations were shallow but regular and not labored. Examination of the heart, abdomen and extremities revealed no abnormalities. The gag reflex was normal. The neck resisted flexion. The white blood count was 11,600 per cu. mm. with a normal differential. The hemoglobin was 15.5 gm. per cent. Urine and stool examinations were normal. A tuberculin 1:1000 test was negative. Other studies showed the blood sugar, 118 mg. per cent; non-protein nitrogen, 32 mg. per cent; CO2 combining power, 26.1 vol. per cent. The cerebrospinal fluid pressure was 165 mm. H₂O; protein, 57 mg. per cent; sugar, 70 mg. per cent. There were 15 cells, all mononuclears. Roentgen studies of the chest and skull revealed no abnormalities. An electroencephalogram taken the day after admission indicated "severe, generalized cerebral dysfunction."

Most observers were of the opinion that the findings were indicative of intracranial neoplasm, but during a review of the history with the patient's parents it was brought out that he had been in contact with mumps infection two weeks prior to admission. Part of the cerebrospinal fluid was then injected intraamniotically into seven day old embryonated eggs. The serum was stored for later tests. The patient remained comatose for the next two days without any significant change in his general condition. Treatment was asymptomatic and consisted in the main of intravenous fluids. After about forty-eight hours he began

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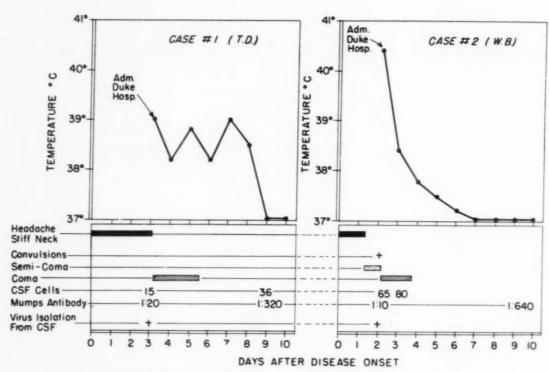


Fig. 1. Salient clinical and laboratory findings in two cases of sudden coma induced by mumps virus.

to regain consciousness and was virtually asymptomatic within twenty-four hours of the onset of the recovery phase. A chicken cell hemagglutinating agent was recovered from the inoculated eggs and proved to be mumps virus when tested against a reference mumps antiserum. Antibody studies on the serum showed an initial mumps antihemagglutinin titer of 1:20 with a rise to 1:320 in a later serum sample. Careful examination of the patient at the time of discharge failed to reveal any detectable physical impairments. The parents stated that, at this time, his mental status was equal to that prior to the present illness.

CASE II. W. B., a sixteen year old white schoolboy, was brought to the Duke Hospital about sixteen hours after the development of semicoma and one hour after a generalized convulsion. The parents stated that the boy was in good health until about two days prior to the present admission, at which time he complained of a mild headache and pain in the neck. This apparently was not severe enough to restrict his activities so that neither the parents nor the patient were alarmed at this time. About sixteen hours prior to admission the patient was found in bed in a semicomatose condition, unable to speak. A local physican was consulted but when the patient had a convulsion and lapsed into coma he was referred to the Duke Hospital immediately.

On examination the blood pressure was 110/70 mm. Hg, pulse 84, respirations 16, and temperature 40.3°c. (Fig. 1.) He was a tall, slender boy, unrespon-

sive to his surroundings and reacting only slightly to deep pain. The neck was slightly stiff. The parotid glands were not enlarged. The respirations were regular and the remainder of the examination, except for the neurological, was not remarkable. All the tendon reflexes were hypoactive but no abnormal reflexes were present nor was there any paralysis. The white blood cell count was 7,100 per cu. mm. with a normal differential. The hemoglobin was 15.6 gm. per cent. The urine was normal. All the blood chemical studies were within normal limits. Examination of the cerebrospinal fluid showed an initial pressure of 240 mm. H₂O with 44 mg. per cent protein and 65 mononuclear cells. The spinal fluid sugar was 50 mg. per cent.

Since this case was very similar to the preceding one, mumps was suspected immediately and appropriate virus isolation and antibody studies were initiated. Further questioning of the parents revealed that, although they had been told by their local physician that the child had had mumps some years previously, the signs and symptoms as they described them were more suggestive of tonsillitis or perhaps a peritonsillar abscess. No history of mumps contact prior to the present illness could be obtained. Talks with the local schoolteacher, minister and others failed to reveal any cases of mumps in the patient's locality. Treatment was entirely asymptomatic. The patient began to regain consciousness after thirty-six hours and was essentially well, although weak, on the third hospital day. Virus was recovered from the spinal fluid and the mumps antibody rose from 1:10 to 1:640 by the time

of discharge. At this time there was no evidence of any physical or mental sequalae.

COMMENTS

Many diverse neurologic symptoms have been associated with mumps virus infections but most papers have tended to stress mumps meningo-encephalitis as a mild or benign complication characterized merely by mild headache. Few deaths from this infection have been reported and, in a review of the literature with the presentation of a single new case, Donohue [1] collected only four instances of fatal mumps meningo-encephalitis which were reasonably well documented. The neurotropism of mumps virus has been clearly demonstrated in experimental animals and the histology of mumps encephalitis in hamsters closely parallels that found in the few human cases studied thus far [2].

The present cases were so far removed from the generally prevailing concept of mumps that this virus infection was not even considered at first. It is true that coma complicating mumps has not previously received much emphasis but careful review of mumps encephalitis cases reported by various authors reveals that drowsiness and delirium are not uncommon [3–5]. Finkelstein reported semicoma in one patient [6]. Since mumps infections are so common in the general population it would seem likely that further studies will show mumps virus coma to be more than a rare occurrence. It must be stressed,

however, that none of the usual stigmas of mumps may be present, thus making the clinical diagnosis most difficult. Another pitfall in the diagnosis of mumps is the misleading history of previous mumps infections when, in fact, such had not occurred. In both cases reported herein the parents insisted that the present illness could not be mumps since the patients supposedly had had this disease many years previously. This was incorrect as the virus studies clearly showed. "False positive" mumps histories are common in my experience.

SUMMARY

Two cases of sudden severe coma induced by mumps virus are reported, both occurring in the absence of parotitis. No physical or mental sequelae complicated these infections.

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Vascular Abnormalities in a Well Functioning Kidney as the Cause of Long-Standing Severe Juvenile Hypertension, Cured by Unilateral Nephrectomy*

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Many cases of hypertension caused by unilateral renal disease have been reported, in which cure has been effected by nephrectomy [1]. In most of these cases the affected kidney was decidedly inferior to its counterpart, as shown by preoperative functional and x-ray studies as well as by the postoperative pathological examination. The underlying condition was usually pyelonephritis, malformation of the urinary tract or obstruction of the arterial blood supply severe enough to cause structural and functional damage to the kidney.

However, some cases of nephrogenic hypertension have been described in which abnormalities in the blood supply could be demonstrated only by aortography, whereas the function of the affected kidney was normal [2–11]. In the following report further evidence is presented that abnormalities of the renal artery, without impairment of the function of the kidney, can be the cause of long-standing hypertension and that the operative removal of such a kidney may be justified.

CASE REPORT

On December 30, 1956, a twelve year old boy was examined in the Pediatric Outpatient Clinic of the Rothschild Hadassah University Hospital (Admission No. 39706), suffering from fever and severe headache of four days' duration. His blood pressure was 240/140 mm. Hg; the urine contained albumin and many red blood cells and granular casts. A diagnosis of acute glomerulonephritis was made and the boy was admitted to the pediatric ward. From the previous history it became known that in 1947, at the age of two years, he was treated for facial paralysis, which ap-

peared during an attack of whooping cough. Later in the same year he was hospitalized for about six months with the diagnosis of "chronic nephritis" with hypertension. During the following five to six years he complained frequently of headache, and he was easily fatigued at play and at school. He also had frequent spells of vomiting lasting sometimes for several days, and he was seen on various occasions by pediatricians as well as by a neurologist. There is no record of his blood pressure during this entire period.

In November 1956, about six weeks before admission, his headache became troublesome again, he started to vomit more frequently, and during the last four days before entering the hospital he vomited continually and was unable to eat.

On admission he was found to be normally developed, his weight being 35 kilos. Although he was afebrile, he appeared to be ill, was apathic and even unconscious for various periods of time, during which he responded only to strong stimuli. Occasionally he had muscular twitchings. When conscious, he complained of very severe headache. His blood pressure was 220/160 mm. Hg, his pulse rate was 130 per minute. Heart size and sounds were normal; the lungs and the abdomen were without pathological findings. The neurological examination did not reveal any abnormalities, the cerebrospinal fluid pressure was normal, and chemical and microscopic examination of the fluid did not reveal any abnormalities. The electrocardiogram showed a left ventricular strain pattern. Examination of the eye grounds revealed general narrowing of the arteries with pronounced segmental constriction, increased reflexes and periarteriolar sheathing. X-ray examination of the heart and electroencephalogram were normal. Laboratory examinations revealed the following: 5.2 million red blood cells per cu.mm.; 15.6 gm. of hemoglobin per 100 ml.; 8,300 white blood cells per cu.mm. with a normal differential count. The blood urea nitrogen was 14 mg.

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Table 1
CREATININE CLEARANCES DETERMINED SEPARATELY FOR THE RIGHT AND THE LEFT KIDNEY*

	Right			Left		
	Volume (ml./min.)	Creatinine Concentration (mg./ml.)	UV P	Volume (ml./min.)	Creatinine Concentration (mg./ml.)	UV P
First period	0.16 0.26	130 110	35.3 49	1.13	16.4 24.2	31.4 44.2

*To correct for leakage outside along the ureteric catheters, the bladder was rinsed at the end of each collection period with a known quantity of water, and the urine thus collected was distributed between the two sides

according to the formulas: x + y = b; $x = b \times \frac{R - B}{R - L}$, where x and y are the unknown leaks from the right and left

side, b = urine collected from the bladder, R, L and B the creatinine concentrations determined in the urines from the right and the left ureteric catheters and the bladder respectively. As the manipulation of the ureteric catheters may give rise to ureterorenal reflexes of varying intensity, it should be noted that the values for the urinary volumes and the creatinine concentrations may not reflect the true conditions, which would obtain in the undisturbed kidneys.

per cent, sodium, 142 mEq./L.; chloride, 88 mEq./L.; potassium, 2.6 to 3.0 mEq./L., CO₂ combining power, 21.7 mEq./L. Urinalysis: albumin, 4-plus; the sediment contained 5 to 10 red blood cells and a few hyaline and granular casts per high power field.

The child was given a salt-free and protein-poor diet and was treated with analgetics and sedatives. Magnesium sulfate and Rauwolfia preparations were given intramuscularly. During the following few days he passed normal amounts of urine and the urinary findings became entirely normal. The blood urea remained low, and the serum potassium and chloride, which were lowered during the first days of hospitalization, returned to normal values after the patient had stopped vomiting. However, the blood pressure continued to be elevated to about 190/100 mm. Hg in spite of the treatment. The complaints of headache persisted.

The possibility was discussed that the child might be suffering from hypertensive vascular disease, and that the urinary findings which were present on admission might have been caused by this disease rather than by acute nephritis. A re-evaluation of the findings recorded during the first hospitalization in 1947 also seemed to support the assumption that the child had been suffering even then from hypertensive vascular disease: the prominent features of his illness had been excessive hypertension with occasional readings as high as 230/190 mm. Hg, severe and prolonged attacks of vomiting, transitory facial paralysis, and fundus changes more characteristic of hypertension than of nephritis. The urinary findings at that time were only occasional albuminuria and rarely a few red blood cells and granular casts. Moreover, his blood urea nitrogen had been normal, and only once, after prolonged vomiting, did it reach the level of 43 mg.

per cent. X-ray examination of the kidneys in 1947 had shown normal excretion on both sides with a smaller kidney on the right side.

Further examinations, aimed at elucidation of the nature of this hypertensive disease, revealed a twentyfour-hour excretion of pressor amines (epinephrine and norepinephrine) in normal amounts, and negative results with a regitine test on two occasions. Kidney function tests resulted in the following values: glomerular filtration rate (inulin clearance) = 120 ml./minute, effective renal plasma flow (PAH-clearance) = 725 ml./minute, tubular excretory mass (Tm-PAH) = 72.5 mg./minute (all figures corrected to body surface of 1.73 m²). Intravenous pyelography showed good excretion on both sides. The right kidney appeared to be somewhat smaller than the left and the upper calyx on the right side showed some questionable deformity. A similar finding was obtained on retrograde pyelography. No tumor shadows in the kidney region were seen.

Separate creatinine clearances carried out prior to the retrograde pyelography gave the results shown in Table 1.

As intravenous and retrograde pyelography had given rise to some suspicion concerning the right kidney, retrograde aortography was performed. On the first exposure ("arterial phase") a very thin renal artery was seen on the right side, in front of the first lumbar vertebra, as well as a bean-sized shadow in the direction of the right renal pelvis. Some fine contorted vascular shadows in the region of the right renal pelvis were visible. The left side was normal. (Figs. 1 and 2.) These findings were interpreted as indicating a narrowing of the right renal artery with poststenotic aneurysmic dilatation and with multiple collateral vessels in the region of the right kidney.



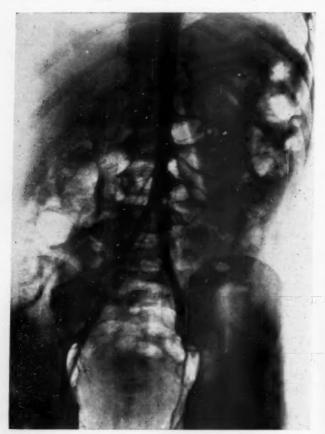


Fig. 1. Arterial phase of retrograde aortography. Note absence of renal artery on the right side, with oblong shadow to the right of the first lumbar vertebra.



Fig. 2. Later exposure. In addition to the oblong shadow visible in Figure 1, two more shadows are now visible, representing the upper calyces.

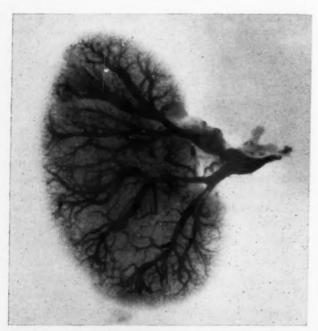


Fig. 3. Excised kidney, filled with lipiodol. Note thin portion of the artery close to the surgical cut and the two dilatations in the main renal artery and in the artery leading to the upper part of the kidney. Also note the additional shadows in the hilar region, representing collateral vessels.

On the basis of these findings surgical exploration of the right kidney was performed on April 30, 1957. The right kidney was found to be somewhat smaller than usual for the age of twelve years, but otherwise appeared entirely normal. On dissection of the hilus a very small renal artery was found which revealed near its entry into the renal parenchyma, a dilatation measuring 1 cm. in length and 0.5 cm. in width. Weak pulsation only, accompanied by a thrill, could be felt on palpation. An artery leading from this dilatation to the upper part of the kidney also appeared to be somewhat dilated. As the preoperative diagnosis of an aneurysm of the right renal artery seemed to be confirmed by these findings, this kidney was extirpated.

Prior to the pathological examination the extirpated kidney was injected with lipiodol. The x-ray obtained showed clearly the narrow part of the renal artery, close to the surgical cut, and two dilatations in the main branches of the artery. (Fig. 3.)

The pathological findings were as follows: The kidney measured 9 by 6 by 3 cm. with a non-adherent capsule and a smooth outer surface. The outer diameter of the renal artery at the point of the surgical cut, 2 cm. from the hilus, was about 2 to 3 mm. A few millimeters distal to the cut the artery was dilated to a width of 5 mm. for a length of about 8 mm. At this point the artery divided into two large branches, one

leading to the upper pole of the kidney revealing another, somewhat smaller dilatation. In the lower branch and in the larger arteries inside the kidney no gross abnormalities were found. Several small additional blood vessels were found in the hilar region, some of them leading directly to the anterior and posterior surface of the kidney. At microscopic examination the renal artery revealed considerable fibrinous thickening of the intima in the vicinity of the surgical cut. Beyond this point and in the region of the dilatation all three layers were well preserved, but in some places the media appeared thinner than usual. The renal parenchyma did not show any structural changes, except a few small foci of lymphocytic infiltration. The microscopic appearance was identical in many sections taken from different areas of the kidney. The small blood vessels were normal, without signs of arteriosclerosis.

The anatomical diagnosis was stenosis of the right renal artery with poststenotic dilatation.

The postoperative course was entirely uneventful. The blood pressure, which prior to the operation was 220/160 mm. Hg, dropped gradually during the week following the operation, with occasional rises up to 190/130 mm. Hg. From the tenth day onward all the readings were approximately 135/85 mm. Hg. On the fifth postoperative day the boy volunteered the information that he was free from headache for the first time in his life.

The child was seen at regular intervals in the outpatient department during the year following the operation. His general health improved markedly, he was free from any complaints, and his weight, which prior to the operation had been 40 kilos, was above 50 kilos. His blood pressure was 110/85 to 125/95 mm. Hg. The eye fundi still showed hypertensive changes, but the electrocardiogram, which had shown left ventricular strain, was entirely normal. The function of the remaining kidney, as can be judged from the 24-creatinine clearance, has improved steadily: before operation, for both kidneys, 119 ml./minute; eight days after the operation 50 ml./minute; one month later 58 ml./minute; eleven months later 133 ml./minute.

When last seen in February 1959, the child continued to be in good health. His weight was 53 kilos. With the patient at rest blood pressure was 125/90 mm. Hg, with occasional initial readings up to 140/100 mm. Hg. The hypertensive changes in the eye fundi, viz. narrowing and tortuosity of the arteries, persisted.

COMMENTS

The case described is that of a twelve year old boy who suffered from infancy, at least from the age of about two years, from severe hypertension. The pathological condition of the affected kidney, diagnosed preoperatively by aortography, and confirmed by the anatomical findings, was a narrowing of the right renal artery with distal dilatations within the branches of that artery. The kidney was only slightly smaller than its counterpart, its blood supply was well maintained through numerous collateral vessels, and no pathological changes within the renal parenchyma could be found. The disease was arrested or cured by unilateral nephrectomy.

It should be pointed out that the excretory function of the affected kidney was normal by the usual clinical criteria: intravenous pyelography showed normal excretion of the contrast medium, the divided clearance study resulted in about equal figures for the creatinine clearance of both sides, and the postoperative creatinine clearance was found to be reduced to about half the preoperative value.

It is of interest, however, to note that in the divided clearance study (Table 1) a much smaller urine volume, with a correspondingly much higher creatinine concentration was obtained from the affected side. It appears probable that this phenomenon, signifying increased tubular reabsorption of water, and possibly also of salt, is the clinical counterpart to acute experiments in dogs in which the reduction of arterial blood supply to one kidney, although too small to cause a measurable fall in glomerular filtration rate, nevertheless causes a reduction in urinary volume and in salt excretion from that kidney [12-15]. In one of the cases of Howard et al. [16] the same observation was made and similarly explained.

As has been pointed out recently by Smith [1], it is probable that in all cases of unilateral disease of the kidney causing hypertension the separate clearances for both sides, including the determination of glomerular filtration rate, renal plasma flow and PAH Tm, will result in significant differences in one or more of these functions. But in many instances such divided clearance studies may be impractical. In such cases if a "normally" functioning kidney shows, on aortography, anatomical changes within the renal artery, the comparison of urinary volume, creatinine and salt concentration from both sides, may furnish evidence that the blood supply to one kidney is diminished. This evidence may occasionally be of importance if the diagnosis of nephrogenic hypertension is suspected on the basis of aortographic findings, and nephrectomy is considered.

With respect to the indications for nephrectomy, it appears that the cases of hypertension with malformation in one of the renal arteries should be singled out from the larger group of

cases of nephrogenic hypertension, and different criteria for nephrectomy should be used. Whereas in the general group, according to some authors [17–19], the chances of curing or arresting the hypertensive disease are so slim that only a definitely diseased kidney with largely impaired function should be removed; the situation may be different for cases with renal arterial obstructions and aneurysmal dilatations. In a few of these cases impressive results have been achieved by the removal of a kidney with well preserved function but with structural alterations of the renal artery [2–11], and these instances, together with the case presented here, seem to justify the operative removal of such a "normal" kidney. It need hardly be stressed that such an operation should be carried out only if the other kidney shows a normal function and is free from similar structural arterial changes.

Another point of interest in the case presented is the long duration of the hypertensive state. It has been stated repeatedly that the nephrogenic hypertension must be of relatively recent origin in order to justify nephrectomy [19,20], but some authors have had gratifying experiences with nephrectomy in cases of longstanding nephrogenic hypertension [3]. It appears reasonable to assume that in the case presented here the early age at which the arterial obstruction must have occurred favored the formation of collateral vessels to the hilus of the affected kidney, and that thereby this kidney was protected from ischemic damage.

SUMMARY

The case is presented of a twelve year old boy who suffered for at least ten years from severe hypertension. Narrowing of the right renal artery, with poststenotic dilatation, was diagnosed by aortography. Nephrectomy resulted in a cure of the disease.

The fact is stressed that in this case the affected kidney was normal in function, as shown by intravenous pyelography and by separate creatinine clearance determinations. The pathological examination of the operative specimen also showed an entirely normal kidney. The only difference found in the function of both kidneys was a smaller urinary volume with a correspondingly higher creatinine concentration on the affected side. The mechanism of this finding and its possible significance for the diagnosis and indication for surgery is discussed.

Acknowledgment: Our thanks are due to Dr. S. Z. Rosenberg for performing the aortography, and

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The Appearance of Histiocytes in the Blood in Subacute Bacterial Endocarditis*

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HISTIOCYTES are sometimes found in the blood of patients with subacute bacterial endocarditis. Frequently the monocytes are increased in number; less often a few phagocytic cells are seen; and rarely the blood, particularly from the ear lobe, is filled with histiocytes phagocytizing the blood elements. In the patient reported here, the diagnosis of endocarditis was made only after the appearance in the blood of large numbers of bizarre histiocytes phagocytizing red and white blood cells and platelets.

CASE REPORT

A forty-six year old white man was admitted to the New York Hospital for the first time in March 1950 complaining of easy fatigue, exertional dyspnea, and weight loss of 35 pounds over a period of six weeks. There was a daily temperature elevation to as high as 39°c. For five months he had noted the presence of petechiae on the legs where he wore an Ace bandage.

These petechiae were seen on physical examination. The heart was not enlarged. At the apex, there was a moderately loud, harsh, systolic murmur and, at times, a soft diastolic murmur. The liver and spleen were firm and extended 6 cm. below the costal margin. The lymph nodes were not enlarged.

The hemoglobin concentration was 10.8 gm. per 100 cc. and the red blood cells numbered 3,700,000 per cu. mm. There were 5,400 white blood cells per cu. mm. with 58 per cent lymphocytes and 2 per cent monocytes. Platelets were adequate. Bone marrow aspiration was essentially normal. The bleeding, clotting and prothrombin times were normal. Results of the tourniquet test were slightly positive. The osmotic fragility of the erythrocytes was normal. A Coombs' test was positive. The stool urobilinogen was 722 Ehrlich units per 100 gm. (normal: up to 350 units with a hemoglobin of 14.5 gm. per cent). The bilirubin was 0.9 mg. per 100 cc. serum; thymol turbidity was elevated to 12 units, and cephalin flocculation to 17 units. Serum proteins were 7.4 gm. per 100 cc. with 3.6 gm. albumin and 3.8 gm.

globulin per 100 cc. The urine contained rare red blood cells. Six blood cultures, some incubated for as long as twenty days, were sterile.

No specific treatment was given. The fever decreased, the anemia improved, and on discharge after thirty-seven days the patient felt much better. The diagnoses were hepatosplenomegaly, probably as a result of lymphoma, and secondary hemolytic anemia.

Three months later the patient was readmitted because of recurrence of symptoms and onset of a heavy sensation in the left upper quadrant of the abdomen. New findings were clubbing of the fingers and evidence on x-ray examination of slight left pleural effusion. Biopsy of the sternal bone marrow revealed hypoplasia. Anemia persisted and the white blood cells were unchanged The Coombs' test now revealed negative results. The serum protein was further elevated to 8.9 gm. per cent with 3.8 gm. per cent albumin and 5.1 gm. per cent globulin. Result of three blood cultures were negative. The patient received 1 L. of whole blood. The anemia improved, the effusion disappeared, and again he felt better upon discharge seventeen days after admission.

The third admittance was in October 1950 because of fatigue and high fever. The appearance of 69 per cent histiocytes in the peripheral blood smear, obtained from the ear lobe, had been noted in the course of follow-up. Total white blood cell count was 17,300 per cu. mm. and 12 per cent of the cells were lymphocytes. A few days later, blood from the finger showed a white blood cell count of 6,700 per cu. mm. with 61 per cent lymphocytes (?) and 2 per cent monocytes. (Table 1.) The anemia was unchanged. The firm spleen was larger and tender. Examination of the heart revealed aortic and mitral systolic murmurs and an aortic diastolic murmur transmitted down the left sternal border. There was marked clubbing of the fingers and toes. Serum protein was 9.1 gm. per cent with 3.2 gm. per cent albumin and 5.0 gm. per cent globulin. The presence of a cryoglobulin was demonstrated. L. E. cells could not be found. Biopsy of the sternal bone marrow revealed hyperplasia; punch biopsy of the spleen was not diagnostic.

gm. per 100 cc. with 3.6 gm. albumin and 3.8 gm. Because of the demonstration of histiocytosis, *From the Department of Medicine, The New York Hospital, Cornell Medical Center, New York, New York.

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TABLE I BLOOD COUNTS

	Dates								
Blood Cells	9/28/50	10/11/50	11/8/50	11/15/50	11/28/50	12/20/50	12/20/50	12/20/50	
Erythrocytes, per cu. mm	3,800,000	3,900,000	3,700,000			4,100,000	* * * * * * * * *		
Hemoglobin, gm. per cent Hematocrit, per cent		10.7	10.5	9.4		10.3			
Blood source	Ear lobe	Finger	Ear lobe	Ear lobe	Ear lobe	Ear lobe,	Ear lobe, left	Finger	
White blood cells, per cu. mm	17,300	6,700	6,600	5,200		8,000	9,600	4,600	
Lymphocytes, per cent			17	15	26	41	48	34	
Monocytes, per cent				0	0	1	2	2	
Eosinophils, per cent				1	9	2	1	3	
Basophils, per cent			0	0	1	2	0	0	
Band forms, per cent			15	28	15	9	13	17	
Neutrophils, per cent				15	36	26	23	41	
Histiocytes, per cent			50	41	13	18	13	3	

occasionally noted in subacute bacterial endocarditis, and because of the course and changing cardiac signs, the patient was started on treatment for subacute bacterial endocarditis, even though results of previous blood cultures had all been negative. Nine additional cultures were obtained before therapy was instituted: penicillin-G sodium 3,000,000 units per day; dihydrostreptomycin 2 gm. per day, and Aureomycin® 2 gm. per day. One of the blood cultures taken before treatment at the time of the highest temperature spike subsequently grew out an enterococcus which was inhibited in vitro by 1.6 units per cc. of penicillin and 42 gammas per cc. of streptomycin. Penicillin was stopped after seventeen days because of a rash which then disappeared. Dihydrostreptomycin and Aureomycin were administered for forty-two days.

During the period of treatment the temperature became normal, the spleen decreased appreciably in size and tenderness, tests of liver function improved, the serum globulin decreased, and the histiocytes disappeared from the blood of the ear lobe. Eight blood cultures following treatment were sterile.

The patient moved from the New York area. We learned that seventy-two days after discharge cardiac failure developed, which at first was adequately controlled by medications. However, he died in cardiac failure two and a half years later. Although no autopsy was obtained, there had been no clinical evidence of relapse of the infectious process after discharge.

DESCRIPTION OF THE UNUSUAL CELLS

The bizarre cells which appeared in the blood, particularly that obtained from the car lobe, may best be called histiocytes or macrophages. (Figs. 1 and

2.) They were of two types. First, there were large cells measuring up to 20 by 30 microns in diameter and usually containing cytoplasmic inclusions. Some cells contained two nuclei. The nuclei were large, oval or round, and occasionally indented. The chromatin pattern was sieve-like and similar to that seen in a reticulum cell. A single, very large, distinct nucleolus was often present. Cytoplasm was abundant and finely granular, and frequently stretched out in long thin streamers. All stages of degenerating red blood cells, lymphocytes and neutrophils could be seen within the cytoplasm. Inclusions resembling degenerating platelets were also seen. In addition to the degenerating cells, there were round cytoplasmic bodies, 2 microns or less in diameter, which stained dark blue with Wright or Wright-Giemsa stain. The cytoplasmic granules took a positive peroxidase stain only when it was obvious that they were related to a phagocytized neutrophil.

The second type of cell was smaller and appeared to be an intermediate form between the first type of cell described and a typical monocyte. These cells were occasionally in large clumps or in syncytial arrangement. The nuclei had a less reticular chromatin pattern, and were frequently lobulated or kidneyshaped. The cytoplasm had moderate numbers of granules, usually azurophilic, which were more abundant at the region of the nuclear indentation. Some typical monocytes were also seen.

REVIEW OF THE LITERATURE

In 1907 Van Nuys [1] and Bartlett [2] of the Massachusetts General Hospital each reported on a patient who had large numbers of phagocytic cells in the peripheral blood, particularly

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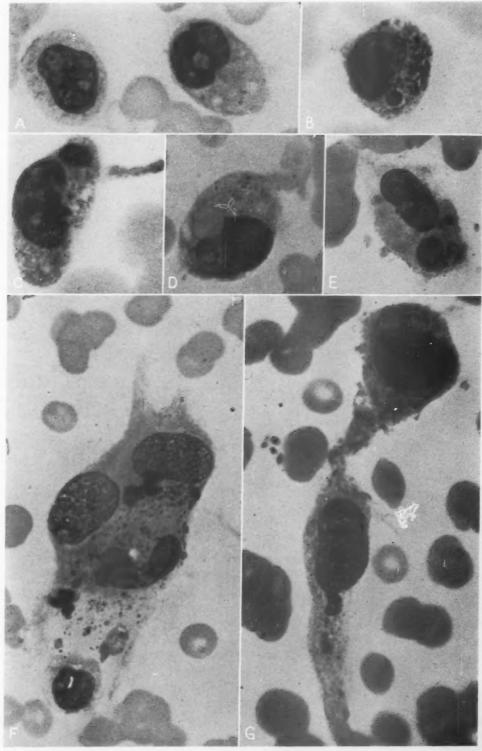


Fig. 1. Histiocytes in blood smear from ear lobe of patient with subacute bacterial endocarditis. Wright stain. Magnification × 1400. A, histiocytes having the appearance of monocytes. B and C, histiocytes with unidentified material in the cytoplasm. D, histiocyte with red blood cell in cytoplasm. E, histiocyte with lymphocyte in cytoplasm. F, giant multinucleated histiocyte with neutrophil and other material in cytoplasm. G, large histiocytes showing drawn out cytoplasmic streamers.

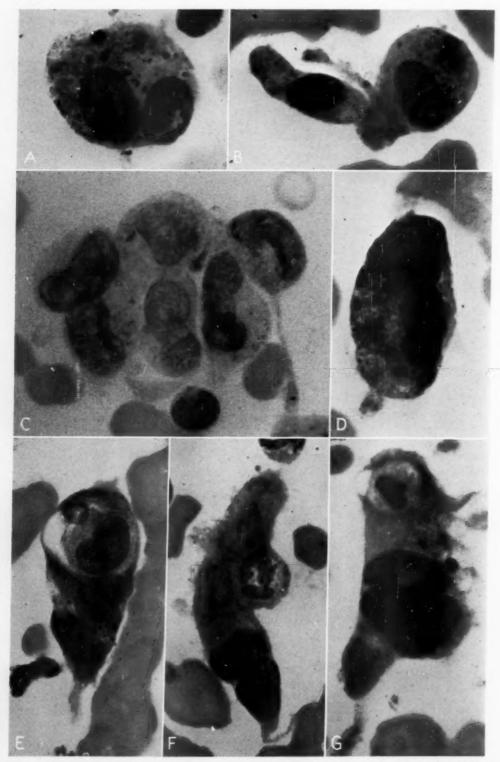


Fig. 2. Histiocytes in blood smear from ear lobe of a patient with subacute bacterial endocarditis. Wright stain. Magnification \times 1400. A, multinucleated histiocyte with pigment granules in the cytoplasm. B, histiocytes, one having a degenerating neutrophil in the cytoplasm. C, clump of histiocytes having elongated nuclei. These cells resemble normal endothelial cells. D, giant multinucleated histiocyte with prominent nucleolus. E, F and G, giant multinucleated histiocytes with other blood cells in the cytoplasm.

in blood from the ear lobe. From their excellent descriptions of the cells and the accompanying photographic reproductions it is clear that the cells they described are identical with those seen in the blood of the patient reported here. Van Nuys' patient was a fifty-five year old man who complained of swollen feet and exertional dyspnea. Examination revealed clubbing of the fingers, edema of the feet, rales in the lungs, aortic regurgitation, hepatosplenomegaly, and small abdominal masses. The abnormal blood cells varied greatly in number from day to day, and constituted as many as 40 per cent of the total white blood count even during an acute infection when the white count rose to 100,000 cells per cu. mm. Because of their morphology and occasional syncytial arrangement, Van Nuys postulated that the unusual cells were endothelial in origin. He suggested that the patient might have leukemia.

Bartlett's patient, who was later studied and reported by Rowley [3,4] was a twenty-seven year old man in whom symptoms of cardiac failure developed. Examination revealed fever, marked clubbing of the fingers, aortic and mitral insufficiency and hepatomegaly. Bartlett found that the unusual cells were noted in blood from the ear lobe and not in blood from the fingers, toes or top of the ears. There was considerable variation in the numbers of phagocytic cells obtained at the same time from the right and left ear lobes. On one occasion the white blood cell counts in the blood from the right and left ear lobes were 84,000 and 262,000 per cu. mm. respectively. Simultaneous red cell counts were the same in blood from both ear lobes. Later, when the peripheral white blood cell count rose to 425,000 per cu. mm. (700,000 to 800,000 per cu. mm. in blood from the ear lobes) the abnormal cells were seen in smears from all locations.

Rowley observed phagocytosis through a microscope fitted with a warm stage. She noted that "there was active phagocytosis of red and white cells, not only by the large lymphocytes, but also by the polynuclear cells and by every variety of leukocyte known in normal blood." She described the manner in which phagocytosis took place and the process of destruction of phagocytized material. She believed that the anemia of the patient could be accounted for on the basis of phagocytosis and destruction of red cells. *In vitro*, the patient's blood was able to stimulate phagocytosis in blood from other

persons. Phagocytes were obtained from the ear vein of a guinea pig two weeks after the animal had been inoculated subcutaneously with 5 drops of the patient's blood. The phagocytic cells from the patient were shown to have extraordinary vitality even after more than three months in vitro.

Both of these patients were thought to have a form of leukemia. However, it is interesting to note that they also had many features of endocarditis, and it is conceivable that the high white blood cell counts were, in reality, leukemoid reactions.

Suntheim [5], Leede [6] and Schilling [7] were the first to recognize the association of the unusual cells in the peripheral blood with the diagnosis of endocarditis. Their observation has been confirmed many times [1–27] and in the European literature bizarre cells of this type have come to be designated as "endocarditis lenta" cells. In a recent review of 200 cases of subacute bacterial endocarditis studied at the Mayo Clinic, Parsons, Cooper and Scheifley [25] concluded that of 122 instances in which peripheral blood smears were examined, reticulo-endothelial cells were found in thirty-seven instances and phagocytic cells occurred in eleven.

Phagocytic cells have been described in the peripheral blood in many diseases other than endocarditis. These references have been summarized in Table 11. Endothelial cells are occasionally found in peripheral blood smears of normal persons [44]. However, from the review of the literature, we gained the impression that the presence in the peripheral blood of many large, bizarre histiocytes phagocytizing all of the other blood elements is virtually pathognomonic of endocarditis. On the other hand, the appearance of occasional mononuclear cells or histiocytes ingesting red blood cells or other material occurs in many other tabulated diseases, as well as in endocarditis. Hurxthal [21] came to the same conclusion.

PATHOGENESIS OF THE UNUSUAL CELLS

The source of the unusual histiocytes in the peripheral blood has been debated. Several observers found a generalized proliferation of the endothelium of the small blood vessels in patients with subacute bacterial endocarditis. They believed that the endothelium of the small blood vessels became transformed into cells with phagocytic properties. Such a generalized patho-

TABLE II
REFERENCES TO DISEASES IN WHICH HISTIOCYTES HAVE
BEEN DESCRIBED IN THE PERIPHERAL BLOOD

Disease	References	
Typhoid fever	[9,28–31]	
Typhus	[9,16]	
Septicemia	[32,33]	
Tuberculosis	[7,33,34]	
Atypical sepsis	[7,33,34]	
Smallpox		
Cholera		
Malaria	[3,7,16,19,32,37]	
Recurrent fever	[16]	
Trypanosomiasis	[37]	
Trichinosis	[33]	
Rheumatic fever	[33]	
Anaphylaxis	[33]	
Dementia paralytica	N N	
Anemia	[9,28,32,33]	
Hemolytic anemia	[38–39]	
Agranulocytosis		
Thrombocytopenic purpura		
Lymphoblastoma		
Leukemia	1	3]
Carcinoma	1 4	

logic process in subacute bacterial endocarditis has not been recognized in this country, except for recent reviews by Kerr [45] and by Daland [26] and her associates. However, considerable evidence for such a concept is found in the European literature.

Ottander [19] reporting on the microscopic findings in two patients with endocarditis, found a generalized reticuloendothelial reaction. A section of the ear lobe showed a striking reaction—hyperplasia of the endothelial cells, not only in the markedly dilated capillaries, but also in the veins and to a smaller extent in arteries. The lumina of blood vessels in some areas contained hyalin-like masses, interpreted as remnants of exfoliated endothelial cells. Several lumina were totally obliterated. There was also proliferation of adventitial cells. Spleen, liver and bone marrow had evidence of similar proliferation of endothelium.

The findings in the ear lobe were confirmed by Bykova [46], who concluded that the endocarditis per se was only part of a more generalized process. Schilling [7] had previously reported proliferation of the reticuloendothelial cells of the liver and spleen in endocarditis. Hess [9,10] postulated that streptococcal toxin induced generalized vascular changes affecting the endo-

thelium, possibly explaining the frequency of embolism and thrombosis. Kartaschowa [16] stated that the atypical cells probably originated from the endothelium of the smallest blood vessel walls. The histologic findings in thirty patients with endocarditis were reported by Istamanova [23] who concluded that in the subacute form there was activation and hyperplasia of the entire reticuloendothelial system. Merklen and Wolf [47] also considered that the endothelium throughout the body was involved, and that endothelial proliferation with secondary thrombosis was a fundamental pathologic process in subacute bacterial endocarditis.

That histiocytes, often in large and fluctuating numbers, are found more frequently in blood from the ear lobe than in blood from the finger was recognized in the first cases reported and has been frequently confirmed. Bittorf [8], who was of the opinion that the endothelial cells originated from the endothelium of the peripheral blood vessels rather than from the spleen or liver, mentioned that the number of phagocytes obtained from the blood of the ear lobe could be increased by first massaging the ear lobe and that the phagocytes were particularly numerous in the first drop obtained. Daland [26] and her associates in this country have attempted to ascertain not only the source of histiocytes but also the reason for their prevalance in blood drawn from the ear lobe. They recognized the hyperplastic changes reported in the vascular endothelium, particularly of the ear lobe. However, by comparing blood counts made in blood from the ear lobe, finger and vein they were able to show that all types of white cells, not only the histiocytes, were increased in number in the blood from the ear lobe. They explained this discrepancy on a "greater selective filtering capacity of the vascular bed of the ear lobe compared to that of the finger tip."

EXPERIMENTAL WORK

Because of the hyperglobulinemia manifested by this patient, the possibility that the phagocytosis might be due to an opsonin was considered. Several experiments were conducted in an attempt to demonstrate the presence of an opsonin in the blood before treatment was started.

Blood from the ear lobe was examined under the microscope at 37°c. after staining supravitally with neutral red—Janus green, and

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TABLE III
RESULTS OF PHAGOCYTOSIS EXPERIMENTS

			Exper	iment 1	Exper	iment 2
Organism	Blood Specimen	Blood Cell	No. of Phago- cytized Or- ganisms per 100 Neutro- phils Counted	No. of Cells Phagocytizing per 100 Neu- trophils Counted	No. of Phago- cytized Or- ganisms per 100 Neutro- phils Counted	No. of Cells Phagocytizing per 100 Neu- trophils Counted
Alpha streptococcus	Citrated Defibrinated	Neutrophils Histiocytes Neutrophils Histiocytes	55 52 1613 138	7.5 6.5 51 7	*	
Staphylococcus	Citrated Defibrinated	{Neutrophils Histiocytes Neutrophils Histiocytes	116 45 31 0	9 4 8 0	190 300 110* 90*	12 11 15* 10*
Enterococcus	Citrated Defibrinated	Neutrophils Histiocytes Neutrophils Histiocytes	4 0 0 0	1 0 0 0	10 20 0† 0†	2 1 0† 0†
Patient's own enterococcus	Citrated Defibrinated	Neutrophils Histiocytes Neutrophils Histiocytes			6 22 12 0	2 1 1 0

* Total, twenty-one neutrophils counted.

† Total, twenty-five neutrophils counted.

neutral red—pinacyanol. The phagocytic cells were easily identified, but they were not motile and showed no evidence of phagocytosis for periods up to three hours. The polymorphonuclear leukocytes were quite motile in these preparations. Similar studies were made at the edges of hanging drops of blood unstained, and the results were similar.

The patient's plasma (oxalated) was incubated at 37°c. with red cells and buffycoat from normal blood. Specimens of buffycoat from this mixture were smeared at intervals up to ninety minutes and stained with Wright-Giemsa stain. A control preparation containing normal plasma, red cells and buffycoat was studied in the same manner. There was no evidence of active phagocytosis in either preparation.

Studies were also made of the ability of the patient's blood cells to phagocytize bacteria. Ten cc. of blood was drawn from the arm vein of the patient. Citrate was added to half of the specimen; the other half was first defibrinated

with glass beads and then citrate was added Each sample was then incubated in test tubes with one of three microorganisms (sixteen-hour culture) for a period of fifteen minutes at 37°c. In the first experiment, the organisms used were alpha streptococcus, staphylococcus, and enterococcus. In the second experiment, the patient's own organism, an enterococcus, was substituted for the alpha streptococcus. The specimens were agitated by slow rotation on a drum. Coverslip smears were then made from all tubes and stained with Wright's stain. The number of neutrophils and histiocytes phagocytizing organisms were counted, at least 100 neutrophils being counted. Note was also made of the number of organisms in each cell. The results of these experiments are recorded in Table III. Interpretation of an in vitro experiment of this type is difficult. However, under the conditions of the experiment, the patient's own blood cells did not phagocytize the enterococcus (even his own organism) as well; as they did the alpha streptococcus and staphylococcus. Neutrophils and histiocytes both participated in the phagocytosis.

SUMMARY

A report is made of a patient with subacute bacterial endocarditis, whose peripheral blood contained large numbers of histiocytes phagocytizing all the other blood elements. The bizarre cells occurred particularly in blood from the ear lobe. They disappeared after adequate antibiotic treatment. Attempts to demonstrate the presence of an opsonin in the blood were unsuccessful.

Previous reports of such cells are reviewed, and the pathogenesis of the histiocytosis is considered.

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Histiocytosis X*

Chronic Disseminated Form (Schüller-Christian Disease) with Marked Arteriosclerosis in a Young Woman

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Schüller-Christian disease is today considered to represent the chronic disseminated form of histiocytosis X [1]. The lesions of histiocytosis X have been reported to occur in most of the organs and tissues of the body; in many instances such involvement is not apparent clinically and is found only at postmortem examination. The association of marked arteriosclerosis of the abdominal aorta, tibial and femoral arteries in a young woman who has had evidence of Schüller-Christian disease for many years, suggests a possible causal relationship between the two conditions. We have been unable to find any mention of antemortem signs of such advanced arteriosclerosis in a young patient with the chronic form of histiocytosis X and are reporting the case for this as well as other unusual features of her illness.

CASE REPORT

G. G. (KCH No. 122545), a thirty year old Jewish housewife, was admitted to the Medical Service (Division II) of Kings County Hospital for the first time in 1956 complaining of pain in the lower extremities. She stated that at the age of five, lumps (otherwise undescribed) developed on both elbows. When she was six years old a fall resulted in compound fractures of the left tibia and the left elbow, followed by chronic infection of the elbow. Between the ages of seven and eight she had abscesses and draining sinuses of the right elbow. These sinuses continued to drain intermittently until 1942 when at the age of sixteen a curettement of a fistulous tract was performed. The pathological diagnosis was inflammatory granulomatous tissue. Roentgenograms of the long bones, reported to show patchy areas of bone condensation within the cortex of the left humerus, left femur and right humerus, were interpreted as chronic osteomyelitis. X-ray films of the chest and teeth were within

normal limits. No further hospitalization was required until the age of twenty-two, when the patient was again examined because of lumps about the left elbow. A sternal marrow aspiration was interpreted as normal and no Gaucher cells were seen. The patient was discharged with the diagnosis of lipoma of the left elbow and Albright's syndrome.

At the age of twenty-four, during the patient's first pregnancy, there was an increase in the polydipsia and polyuria which, the patient stated, had been present intermittently since childhood. Following a full-term spontaneous delivery there was a reduction in the polydipsia and polyuria to previous levels. Three years later, at the age of twenty-seven, the patient was readmitted to the hospital; a biopsy specimen of the left elbow showed chronic granulation tissue with foam cells, lymphocytes and multinucleated giant cells of the Touton type. A diagnosis of chronic osteomyelitis and pseudoxanthomatous chronic inflammation of subcutaneous tissue was made. X-ray examination of the long bones showed no change from previous examinations; however, calcification of the abdominal aorta and tibial arteries was now apparent. At the age of twenty-eight the patient received radiation therapy to both elbows, resulting in slight improvement in the appearance of the skin lesions. At this time an osteolytic lesion of the left clavicle, not present six months previously, was seen on roentgenograms. During her second pregnancy, at the age of twenty-eight, there was an exacerbation of her constant symptoms of polyuria and polydipsia which did not regress following delivery. A Hickey-Hare test showed a 75 per cent drop in urinary output during the test infusion. Roentgenograms of the skull taken at that time revealed no abnormality. The patient continued to have symptoms of diabetes insipidus but did not seek further hospitalization until the age of thirty when the family moved to New York City. She entered the hospital complaining of pain in both lower extremities of many months' duration and made worse by weight bearing. There

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was no history of any similar illness in any other members of the family.

Physical examination revealed a well nourished young woman in no distress. She appeared somewhat mentally retarded and emotionally labile. Temperature, pulse and blood pressure were within normal limits. She had a florid face with moderately severe seborrhea of the face and scalp. Nystagmus on lateral gaze was present but neither exophthalmos nor papilledema was apparent. There was concentric constriction of the visual fields, confirmed by perimetry. The ears were normal. The patient was edentulous but the gums and mucous membranes were normal. A small, firm, movable lymph node was palpable in the left posterior cervical triangle. Examination of the heart, lungs, abdomen and genitalia revealed no unusual findings. The left arm was shortened by a flexion deformity of 90 degrees at the left elbow. The skin overlying the left elbow was warm, tender, swollen and indurated. There was limitation of motion at the right shoulder. Well-healed scars over the left tibia were noted at the old fracture site. The skin over the lower extremities was slightly atrophic. The dorsalis pedis pulses were diminished bilaterally.

The hemoglobin was 11.4 gm. per cent; the white blood cell count was 9,400 to 13,000 per cu. mm. on several examinations; differential counts were normal with no eosinophils; the erythrocyte sedimentation rate was 43 mm. (Wintrobe). Urinalysis showed constantly low specific gravities ranging from 1.001 to 1.005, but was otherwise within normal limits. Blood urea nitrogen was 9 mg. per cent, fasting blood sugar 94 mg. per cent, the total serum proteins 6.3 gm. per cent with 4.0 gm. per cent albumin and 2.3 gm. per cent globulin, serum calcium 10.4 mg. per cent, serum phosphorus 4.6 mg. per cent, serum alkaline phosphatase 9.6 King-Armstrong units per 100 ml. The urinary calcium excretion was 0.211 gm. per twenty-four hours. The serum sodium, potassium, chloride and CO2 combining power were normal. Serum lipid values are shown in Table 1.

Bone marrow cultures for tubercle bacilli and for pyrogens yielded no growth. Lumbar puncture was performed. The initial pressure was 230 mm. and the spinal fluid was clear containing 22 red blood cells and 6 white blood cells per cu. mm., Kolmer negative, spinal fluid protein 68 mg. per cent, sugar 120 mg. per cent. A Hickey-Hare test was positive for diabetes insipidus and there was a normal anti-diuretic response to administered pitressin.

X-ray films of the chest showed a destructive lesion of the outer third of the left clavicle, but no abnormalities of the lungs, heart or ribs. X-ray films of the skull revealed no areas of rarefaction; the sella turcica was normal. Marked calcification of the abdominal aorta was seen on the lateral film of the spine. (Fig. 1.) Examination of the left arm showed destruction of the elbow joint, lower half of the humerus and proximal halves of the radius and ulna with irregular

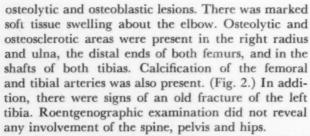
TABLE I

	Ser	Serum			Density < 1.063 (\beta-Lipoproteins)	Density < 1.063 (\beta-Lipoproteins)		Density > 1.063 (α -Lipoproteins)	> 1.063 proteins)	
Patient	Total Choles- terol (mg./100	Total Phosphotenol (mg./100 (mg./100 ml.)	Total Cholesterol Phospholipid Total Cholesterol	Free Cholesterol Total Cholesterol	Total Phospho- Lerol (mg./100 (mg./100 mg.)	Phospholipid (mg./100	tal Cholester	Total Phospho- I Choles- Lipid (mg./100	Phospholipid (mg./100	Total Cholesterol Phospholipid
	mi.)				ml.)			ml.)	m.)	
G. G.†	226	289	0.78	0.26	173.8	155.8	1.12	38.5	125.0	0.31
females)	178	230	0.78	# e e	116	92	1.26	57	134	0.43

* Determinations were performed by Dr. Howard A. Eder employing the method of Havel, Eder and Bragdon [2] † Neutral fat 218 mg./100 ml.



Fig. 1. Lateral projection of the dorsolumbar spine showing calcification of the abdominal aorta, and no abnormalities of the vertebrae.



A biopsy specimen of the left posterior cervical lymph node revealed non-specific chronic inflammation. Open biopsy of the left tibia was performed; the bony cortex was described as thin and friable. Microscopic sections showed the bony trabeculae to be eroded. Masses of fibrous tissue, groups of foamy histiocytes, aggregates of Touton and foreign body giant cells, histiocytes and eosinophils were present. The pathological diagnosis was histiocytosis, Hand-Schüller-Christian type.

The patient was treated with radiation therapy, receiving 1,760 r to the pituitary and 2,400 r to the left elbow. Improvement in the skin lesions was noted, but the diabetes insipidus was unaltered. Regular menstrual periods continued to occur. The polyuria was decreased by the use of intranasal posterior pituitary powder. The patient was discharged but



Fig. 2. Roentgenogram of the lower extremities. Calcification of the tibial arteries is demonstrated. There are osteolytic and osteosclerotic areas present in the shafts of both tibias as well as an old fracture of the left tibia.

repeated episodes of superficial infection of the left elbow led to three brief hospitalizations.

At the age of thirty-one a new area of erythema and induration developed in the region of the left shoulder. The serum cholesterol at that time was 185 mg. per cent with free cholesterol representing 31 per cent of the total. Serum proteins, calcium, phosphorus and alkaline phosphatase values were all normal. A biopsy specimen taken from the skin of the left elbow showed granulation tissue with sclerosis of blood vessels, infiltration with lymphocytes, plasma cells, histiocytes and multinucleated cells containing lipid. Roentgenograms showed a destructive lesion involving the distal one-third of the left clavicle and the coracoacromial process. X-ray films of the right leg revealed many irregularly shaped osteolytic and osteoblastic areas which disappeared during the course of several months' observation. Other radiological findings did not differ from those previously described. The patient was given 2,000 kv. radiation therapy to involved areas as follows: left elbow, 3,984 r; right radius, 6,624 r; left shoulder, 5,220 r. All treated areas of skin showed slight to moderate improvement.

The patient was readmitted to Kings County Hospital for the fifth time at the age of thirty-two

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because of pain in the lower extremities which cleared spontaneously on admission. Physical examination revealed nystagmus more marked on right lateral gaze, papilledema of three diopters bilaterally but no exophthalmos. Examination of the visual fields showed further concentric constriction. The left elbow was fixed in 90 degree flexion with erythema, induration and areas of granulation tissue in the overlying skin. On the left shoulder was a raised, erythematous, indurated lesion 5 cm. in diameter with a central tilcer having a dry, gray-green, rough base. The pedal pulses were absent bilaterally.

The hemoglobin was 10.0 gm. per cent, the white blood cell count was 8,200 per cu. mm. with a normal differential count. Urinalysis showed a low specific gravity with an output of 3 to 5 L. per day. Serum calcium, phosphorus, alkaline phosphatase and cholesterol levels were normal. The electrocardiogram was normal. Complete x-ray examination revealed still further destruction of the left elbow joint with a supracondylar fracture of the disorganized left humerus. No skull lesions were found and the remainder of the radiological examination was similar to previous examinations.

The patient was discharged to clinic follow-up receiving intranasal dried posterior pituitary powder.

COMMENT

The term histiocytosis X has been used to include eosinophilic granuloma of bone, Schüller-Christian disease and Letterer-Siwe disease [1]. The use of the term histiocytosis X implies that these three syndromes are related and are varying forms of one disease process as demonstrated by clinical cases and pathological findings. However, others consider these diseases to be unrelated and disagree with a unitarian hypothesis [3,4].

In the patient presented skin and bone lesions first developed at the age of five and, during the next twenty-seven years, new skin and skeletal lesions appeared at irregular intervals. Although diabetes insipidus has been present in varying severity since childhood, no exophthalmos or visible lesions have appeared in the calvaria. This serves to emphasize the variable nature of the Schüller-Christian triad [5]. The presence of papilledema, nystagmus and constriction of the visual fields, in addition to the diabetes insipidus, implies extensive involvement of the central nervous system. At the present time there is no clinical evidence of pulmonary, hepatic or splenic infiltration.

Marked arteriosclerosis of the abdominal aorta, tibial and femoral arteries, as evidenced

by calcification of these vessels on roentgenograms, has been present since the patient was twenty-seven years old. The arterial pulsations have been diminished or absent since the age of thirty. A sixty-seven year old woman with the acute disseminated form of histiocytosis, reported by Goldner and Volk [6], had extensive atherosclerosis of the aorta; however, because of the patient's age it is difficult to ascribe her vascular disease entirely to her granulomatous disease. Aortic involvement with adventitial xanthomas and intimal atheromas was described by Cavanagh and Russell [7] in a sixtyfour year old woman in whom the disease had been present for four years. Lichty [8] reported the case of a twenty-one month old child with the acute disseminated form of the disease who had marked calcification of the arteries at autopsy, but no histological description is given. Chiari [9] mentions the occurrence of small foci of subintimal cholesterol deposits surrounded by foam cells and collections of round cells about the vasa vasorum of the aortic media in a twentysix year old man with Schüller-Christian disease. Thannhauser [10] refers to perivascular accumulations of endothelial cells in Schüller-Christian disease, but he denies the occurrence of atheromatous lesions such as are seen in hypercholesterolemic xanthomatosis. In a series of twenty-nine patients, Avery, McAfee and Guild [5] do not mention the occurrence of arteriosclerosis.

Analyses of the serum lipids in this patient failed to reveal any striking abnormality. The cholesterol in the high density α -lipoproteins was 18.1 per cent of the total cholesterol, slightly lower than the usual 25 to 30 per cent present in normal young women. The most likely explanation for such advanced arteriosclerosis in this young woman is the occurrence of extensive xanthomatous lesions around the medial and adventitial vasa vasorum, interfering with the nutrition of the vascular endothelium and resulting in the local precipitation of cholesterol and other lipids. Although the lipid deposition is probably secondary to a primary proliferative and granulomatous process, it is one of the striking features of the histological picture as it develops in this disease. At present, the origin of the cholesterol found in the lesions of histiocytosis X is unknown. It has been suggested that the lipid is released locally from involved tissue [7] or is formed intracellularly by macrophages [10]. However, it may arise from the circulating

cholesterol even though the serum levels are within normal limits.

It is well known that the Schüller-Christian form of histiocytosis X is compatible with long survival [5,11], although few cases are reported in the literature with active progressive disease observed over a prolonged period of time. The present case, documented for twenty-seven years, clearly illustrates the relatively benign nature of the disease, as well as the extremely variable course it may take.

SUMMARY

A case of histiocytosis X, Schüller-Christian disease, in a young woman is presented. The unusual features of this patient are the presence of marked arteriosclerosis of the aorta and large arteries of the lower extremities without hypercholesterolemia, and the continual appearance of fresh lesions over a period of twenty-seven years.

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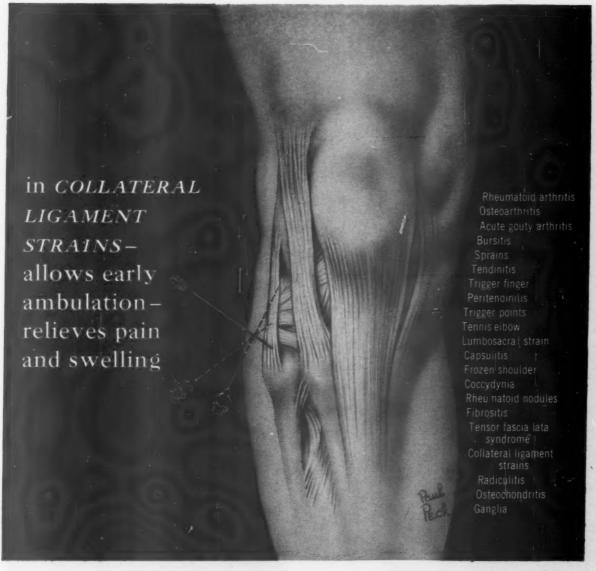
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1. Cass, L.J., et al.: J.A.M.A. 166:1829 (April 12) 1958. 2. Batterman, R.C., et al.: Am. J. M. Sc. 234:413 (Oct.) 1957. 3. Medical Department, Wyerh: Final Report on the Clinical Evaluation of Zactirin.



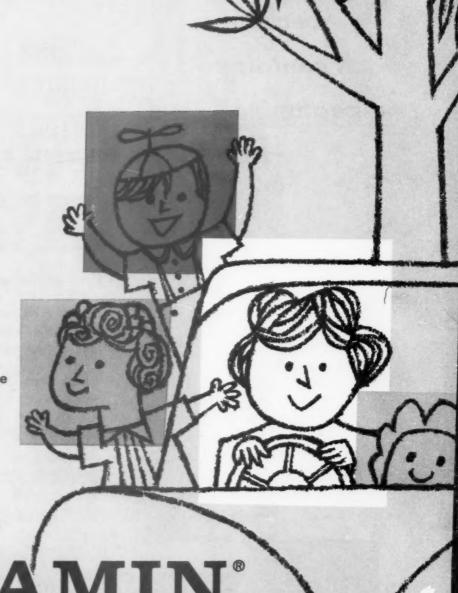
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 Brown, E.B., Ir. The Management of Iron Deficiency Anemia, GP, 2:87 (Feb. 1958).



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*Keith, J.H.: Utilization and Toxicity of Peptonized Iron and Ferrous Sulfate, Am. J. Clin. Nutrition 1:35 (Jan.-Feb., 1957).



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(1) Goldwasser, E.; Jacobson, L. O.; Fried, W., and Pizak, L. F.: Blood 13:55 (Jan.) 1958. (2) Gurney, C. W.; Jacobson, L. O., and Goldwasser, E.: Ann. Int. Med. 49:363 (Aug.) 1958. (3) Korst, D. R.; Bishop, R. C., and Bethell, F. H.: J. Lab. & Clin. Med. 52:364 (Sept.) 1958. (4) Ausman, D. C.: Journal-Lancet 76:290 (Oct.) 1958. (5) Holly, R. G.: Obst. & Gynec. 9:299 (Mar.) 1957. (6) Holly, R. G.: Clin. Obst. & Gynec. 1:15 (Mar.) 1958. (7) Diamond, E. F.; Gonzales, F., and Pisani, A.: Illinois M. J. 113:154 (April) 1958. (8) Hill, J. M.; La Jous, J., and Sebastian, F. J.: Texas J. Med. 51:686 (Oct.) 1955.

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1. Peck, F.B., Jr., and Griffith, R.S.: Antibiotics Annual 1957-1958, Medical Encyclopedia, Inc., p. 1004. 2. Wright, W.W., and Welch, H.: Antibiotic Med. 5:139 (Feb.) 1958.

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"the most important concept is that it is a tubular disease"1

a most important characteristic: effective at the tubular level

In addition to simple glomerular filtration, FURADANTIN is actively excreted by the cells of the tubules.

In the medical management of pyelonephritis, it is important to select an agent such as Furadantin which—in addition to its glomerular filtration—is secreted by the cells of the tubules. Sulfonamides, however, both free and acetylated, are excreted primarily by glomerular filtration² and "the mechanism of excretion of tetracycline is solely a glomerular filtration process without tubular involvement."³

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References: 1. Smith, I. M., and Lenyo, L.: Am. Practitioner 9:78, 1958. 2. Bass, A. D.: Chemotherapy of Bacterial Infections II: Sulfonamides, in Drill, V. A., ed.: Pharmacology in Medicine, New York, McGraw-Hill Book Co., Inc., 1954. 3. Pindell, M. H., et al.: J. Pharm. Exp. Ther. 122:61A, 1958. 4. Jawetz, E., et al.: A.M.A. Arch. Int. M. 100:549, 1957.

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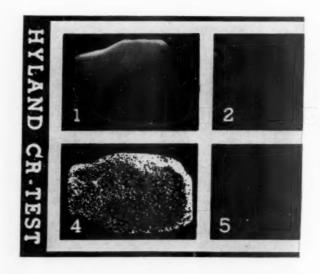
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Kits containing Latex-Anti-C-Reactive Protein Reagent, Glycine-Saline Buffer Diluent for serum dilution, capillary pipettes for serum transfer, and 2 divided glass slides. Each kit sufficient for 60 screening tests. \$10.00 per kit. Also available: CR-TEST Positive Control Serum, 0.5 cc.



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1. Based on six-month National Physicians Survey.



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0.1037 mg.	0.3111 mg.			
Atropine sulfate , 0.019 mg.				
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DR. MONTAGUE: Replace my present prescription for obesity? You'd better have

good reason.

MR. CARR: I have, Doctor. Three of them,

in fact.

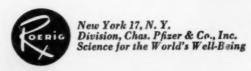
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One capsule half-hour before each meal. Bottles of 100 soft, soluble capsules, this actual size.





DR. MONTAGUE AND MR. CARR DETAIL #1

DR. MONTAGUE: Hello, Mr. Carr. How's your golf?

MR. CARR: About the same as my bowling.

DR. MONTAGUE: The same?

MR. CARR: Same average. 131.

DR. MONTAGUE: Too bad. What's new today?

MR. CARR: Today I bring news of AMPLUS IMPROVED.

DR. MONTAGUE: You've improved AMPLUS? What's AMPLUS?

MR. CARR: Oh good. I get to start from scratch.

DR. MONTAGUE: An antipruritic?

MR. CARR: No. New therapy for obesity.

DR. MONTAGUE: Replace my present prescription for obesity?

You'd better have good reason.

MR. CARR: I have. Three of them, in fact.

DR. MONTAGUE: I'm underwhelmed.

MR. CARR: Always room for improvement, right? AMPLUS, of course,

is d-amphetamine, to control the somatic factor, hunger pangs . . .

DR. MONTAGUE: Of course. Use it all the time.

MR. CARR: ... plus ATARAX, the tranquilizer that supports the psyche

during the critical dieting period, and ...

DR. MONTAGUE: reduces the irritability sometimes caused by d-amphetamine.

Good idea.

MR. CARR: And, since ATARAX is the antisecretory tranquilizer, it

also stops gastric craving.

DR. MONTAGUE: You mentioned another plus.

MR. CARR: Vitamins and minerals.

DR. MONTAGUE: Vi... yes. For a moment I thought you said minerals.

MR. CARR: It was not I. It was Vernon who pointed out that "the

treatment of obesity by diet leaves the medical attendant with an obligation to maintain mineral balance as well as

to avoid avitaminosis."

DR. MONTAGUE: Right. But you usually have some classic summary, Mr. Carr.

MR. CARR: I do indeed. Just worked it out in the waiting room.

AMPLUS IMPROVED can be summarized as:

1 for the psyche ... 2 for the soma
3 to get slim ... 4 the summa'.

DR. MONTAGUE: As always, I question your humor. But I like your product.

What is it again?

MR. CARR: Amplus Improved.

representing
J. B. Roerig and Company
Mr. Carr



4th day



Record of patient with congestive failure, treated at a leading Philadelphia hospital. Photos used with permission of the patient.

marked pitting edema (4+) cleared in 4 days with Esidrix

ESIDRIX IS 10 TO 15 TIMES MORE ACTIVE THAN CHLOROTHIAZIDE

INDICATED IN...congestive heart
failure • hypertension • hypertensive
vascular disease • premenstrual edema
• toxemia of pregnancy • edema of
pregnancy • steroid-induced edema

· nephrosis · nephritis

DOSAGE: Esidrix is administered orally in an average dose of 75 to 100 mg. daily, with a range of 25 to 200 mg. A single dose may be given in the morning or tablets may be administered 2 or 3 times a day.

SUPPLIED: Tablets, 25 mg. (pink, scored); bottles of 100 and 1000. Tablets, 50 mg. (yellow, scored); bottles of 100 and 1000.





L.S., 81-year-old patient with complaint of painless hematuria admitted to hospital on 3/3/59. Past history included congestive heart failure of 15 years' duration. Clinically significant symptoms: expiratory wheezes over entire chest; bilateral coarse rales of both bases; slight abdominal distention (without evidence of ascites); palpable liver 2-3 fingerbreadths below rib cage; bilateral pitting edema (4+) of pretibial and ankle areas. Admission diagnosis: hematuria of unknown origin; arteriosclerotic cardiovascular disease; poorly compensated heart failure; chronic pulmonary fibrosis with pulmonary insufficiency.



Patient was put on regimen of bed rest, moderate salt restriction, digitalis and pulmonary decongestants. When ankle edema, hepatic congestion and rales failed to clear by 3/6, Esidrix 50 mg. b.i.d. was ordered. By 3/8 L.S. had lost 3 pounds. Rales decreased; there was 1 + pitting edema of ankle area only. He felt more comfortable, was able to enjoy reading newspapers and magazines in bed.



Ambulatory on the 4th day of Esidrix therapy, L.S. visited his neighbors down the hall, played checkers with another patient. There was no evidence of ankle edema. By 3/11, patient's weight had dropped 2 mere pounds and rales were gone. Patient tolerated cystoscopy and fulguration of a small bleeding polyp in his bladder on 3/12 very well. On 3/14 he was discharged.

Patient L.S. Date	3/4	3/5	3/6	3/7	3/8	3/9	3/10	3/11	3/12	3/13
Urinary Output (ml.)	840	690	960	2140	1230	660	1220	1350		
Weight (lbs.)	139				136			134		
Esidrix Dosage (mg./day)	0	0	50	100	100	100	100	100	50	100

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1. Brest, A. N., and Likoff, W.: Am. J. Cardiol. 3:144 [Feb.] 1959. 2. Clark, G. M.: Clinical report to CIBA. 3. Dennis, E. W.: Clinical report to CIBA.

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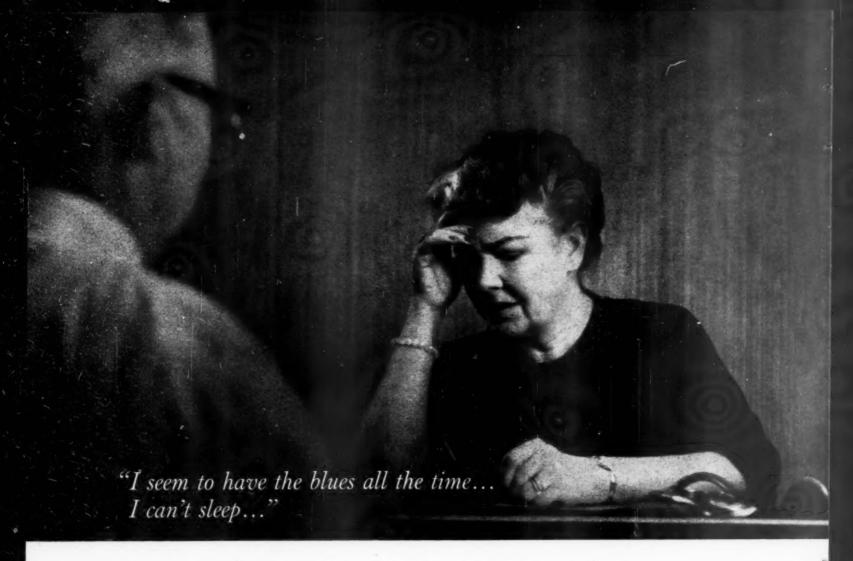
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Pfizer Laboratories Division, Chas. Pfizer & Co., Inc. Brooklyn 6, New York References: 1. Finkelstein, M., et al.: J. Pharmacol. & Exper. Therap. 125:330 (April) 1959. 2. McHardy, G., et al.: Postgrad. Med., in press. 3. Winkelstein, A.: Amer. J. Gastroenterol., in press. 4. Finkelstein, M., et al.: Presented at Fall Meeting, Amer. Soc. Pharmacol. & Exper. Therap., 1958. 5. Leming, B.: Clin. Med. 6:423 (March) 1959.



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References

- 1. Alexander, L.: J.A.M.A. 166:1019, March 1, 1958.
- 2. Current personal communications; in the files of Wallace Laboratories.
- 3. Pennington, V.M.: Am. J. Psychiat. 115:250, Sept. 1958.



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1. Dobson, H., et al.: Ann. New York Acad. Sc. 74:940, 1959. 2. Greenhouse, B.: Paper presented at Conference on Diabinese and Diabetes Mellitus, New York Acad. Sc., Sept. 25-27, 1958, New York, N. Y. 3. Forsham, P. H.; Magid, G. J., and Dorosin, D. E.: Ibid., p. 672. 4. Beaser, S. B.: Ibid., p. 701; New England J. Med. 259:573, 1958. 5. Blöch, J., and Lenhardt, A.: Ann. New York Acad. Sc. 74:954, 1958. 6. O'Driscoll, B. J.: Lancet 2:749, 1958. 7. Hadley, W. B.; Khachadurian, A., and Marble, A.: Ann. New York Acad. Sc. 74:621, 1959. 8. Duncan, G. G.; Schless, G. L., and Demeshkieh, M. M. A.: Ibid., p. 717. 9. Handelsman, M. B.; Levitt, L., and Calabretta, M. F.: Ibid., p. 632. 10. Hills, A. G., and Abelove, W. A.: Ibid., p. 845. 11. Drey, N. W., et al.: Ibid., p. 962.



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References: 1. Graham, W.: Canad. M. A. J. 79:634 (Oct. 15) 1958. 2. Robins, H. M.; Lockie, L. M.; Norcross, B.; Latona, S., and Riordan, D. J.: Am. Pract. Digest Treat. 8:1758, 1957. 3. Kuzell, W. C.; Schafarzick, R. W.; Naugler, W. E., and Champlin, B. M.: New England J. Med. 256:388, 1957.

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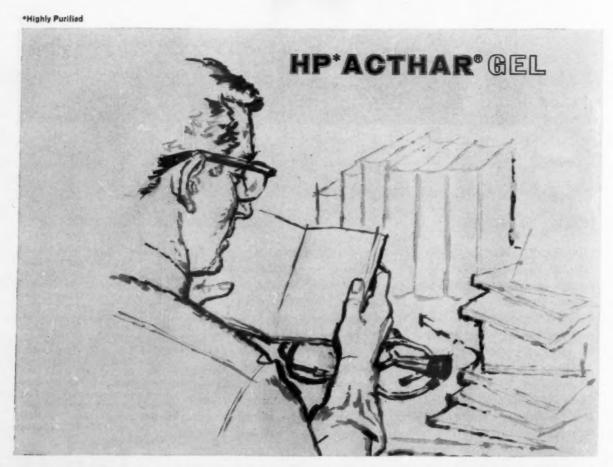
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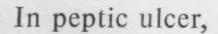
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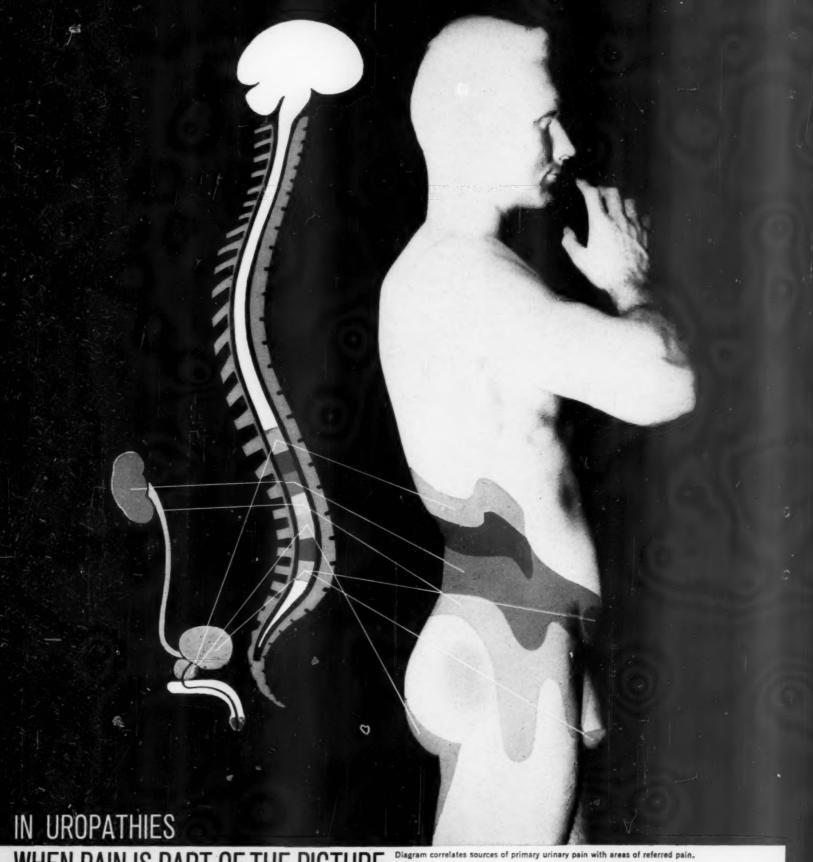
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1. Grossman, A. J.; Batterman, R. C., and Leifer, P.; Fed. Proc. 17:373 (March) 1958.



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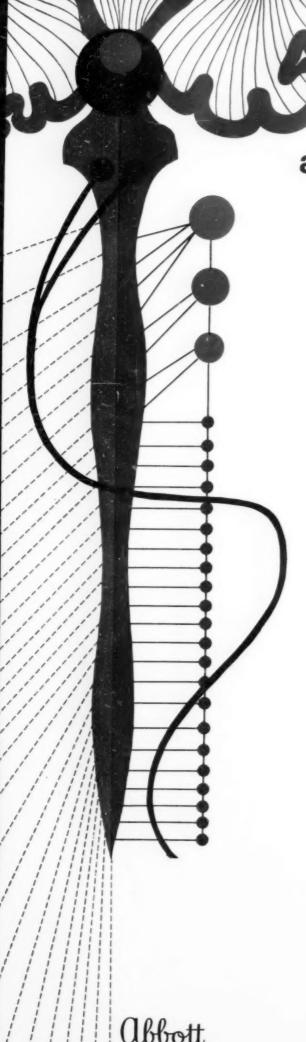


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1. Frohman, I. P., Tranquilizers in General Practice and Clinical Evaluation of Deserpidine, an Alkaloid of Rauwolfia canescens, M. Ann. District of Columbia, 27:641, December, 1958.

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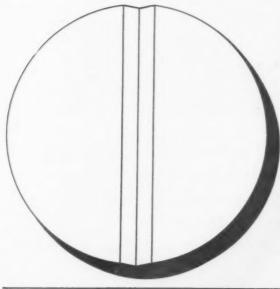


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PENTIDS '400,' each scored tablet contains 400,000 units of penicillin G potassium buffered, bottles of 12 and 100. Twice the unitage of Pentids 200,000 units.

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PENTIDS, 200,000 units of buffered penicillin G potassium per scored tablet, bottles of 12, 100, and 500.

PENTIDS FOR SYRUP, 200,000 units of penicillin G potassium per teaspoonful (5 cc.), 12 dose bottles.

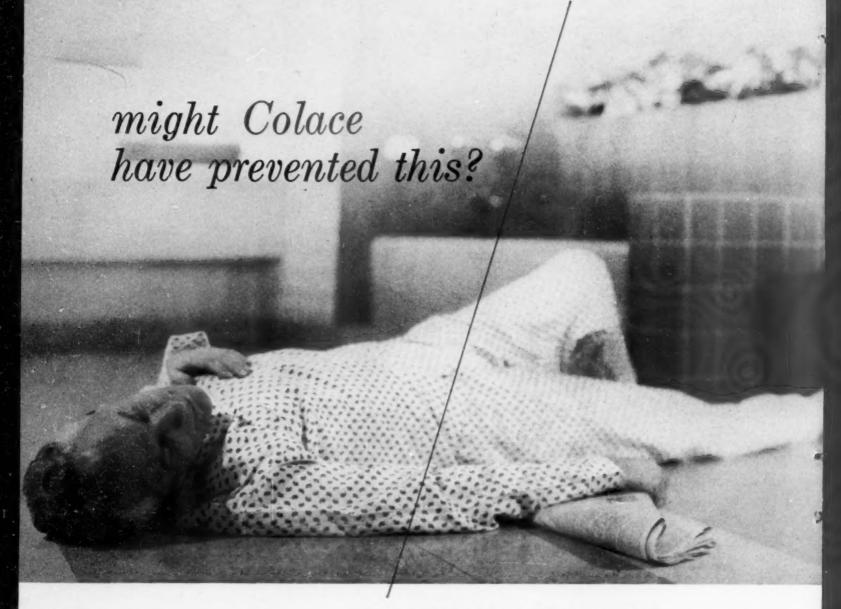
PENTIDS, CAPSULES, 200,000 units of penicillin G potassium per capsule, bottles of 24, 100, and 500.

PENTIDS SOLUBLE TABLETS, 200,000 units of penicillin G potassium per tablet, vials of 12 and bottles of 100.

bettles of 100.

PENTIDS-SULFAS TABLETS, 200,000 units of penicillin G potassium with 0.5 Gm. triple sulfas per tablet, bottles of 30, 100, and 500.

PENTIDS® IS A SQUIBS TRADEMAR



As Dennison¹ reported, "It is our considered opinion that the relief from straining at the stool is, in many instances, life-saving." And, further, "In the handling of bowel problems in cardiac patients, the properties of dioctyl sodium sulfosuccinate closely approach those required of an ideal agent."

Colace

prevents hard, difficult-to-pass stools . . . without laxative action.

available in 3 convenient dosage forms:
capsules (50 and 100 mg.)... for adults and older children
syrup... for children and adults
liquid (drops)... for infants and children



ORAL ANTIDIABETIC THERAPY HAS NOT FAILED FOR THIS PATIENT... THANKS TO DIABINESE*

The specific pharmacologic properties of DIABINESE — high activity, freedom from metabolic degradation, and gradual excretion — permit (1) prompt lowering of elevated blood sugar levels without a "loading" dose, and (2) smooth, sustained maintenance "devoid of...marked blood sugar fluctuations" on convenient, lower-cost, once-a-day dosage. This is the consensus of extensive clinical literature. 1-11 Widespread use of DIABINESE since its introduction has confirmed the low incidence of side effects reported by the original investigators.

Thus, DIABINESE merits first consideration for any diabetic presently receiving or potentially better managed with oral therapy — including many diabetics for whom previous oral agents have proved ineffective.

Supplied: Tablets, white, scored 250 mg., bottles of 60 and 250; 100 mg., bottles of 100.

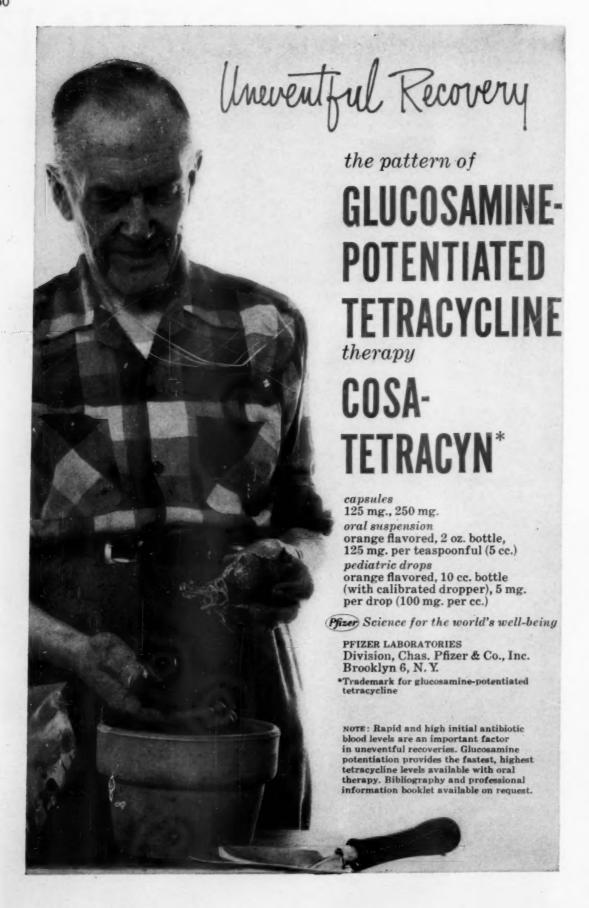
tablets/once-a-day dosage effective in 85% of patients who have become refractory to other oral agents



PFIZER LABORATORIES, Brooklyn 6, New York Division, Chas. Pfizer & Co., Inc.

1. Greenhouse, B.: Ann. NewYork Acad. Sc. 74:643, 1959. 2. Dobson, H., et al.: Ibid., p. 940. 3. Forsham, P. H.; Magid, G. J., and Dorosin, D. E.: Ibid., p. 672. 4. Beaser, S. B.: Ibid., p. 701; New England J. Med. 259:573, 1958. 5. Blöch, J., and Lenhardt, A.: Ann. New York Acad. Sc. 74:954, 1959. 6. O'Driscoll, B. J.: Lancet 2:749, 1958. 7. Hadley, W. B.; Khachadurian, A., and Marble, A.: Ann. New York Acad. Sc. 74:621, 1959. 8. Duncan, G. G.; Schless, G. L., and Demeshkieh, M. M. A.: Ibid., p. 717. 9. Handlesman, M. B.; Levitt, L., and Calabretta, M. F.: Ibid., p. 632. 10. Hills, A. G., and Abelove, W. A.: Ibid., p. 845. 11. Drey, N. W., et al.: Ibid., p. 962.





new for total management of itching. inflamed, inflamed, skin lesions



Mycolog Ointment – containing the new superior topical corticoid Kenalog – re-

duces inflammation,^{3,4} relieves itching,^{3,2} and combats or prevents bacterial, monilial and mixed infections.^{5,7} It is extremely well tolerated, and assures a rapid, decisive clinical response for most infected dermatoses.

"Thirty-one of 38 patients... obtained excellent or good control of dermatological lesions... [Mycolog] was highly effective, particularly in the management of mixed infections. Several recalcitrant eruptions which had not responded to previous therapy were remarkably responsive to the daily application of this preparation over periods of 2 to 3 weeks."

For total management of itching, inflamed, infected skin lesions, Mycolog contains triamcinolone acetonide, an outstanding new topical corticoid for prompt, effective relief of itching, burning and inflammation¹⁻⁴ — neomycin and gramicidin for powerful antibacterial action⁷ — and nystatin for treating or preventing <u>Candida (Monilia)</u> <u>albicans</u> infections.^{6,6}

Application: Apply 2 to 3 times daily. Supply: 5 Gm. and 15 Gm. tubes. Each gram supplies 1.0 mg. (0.1%) triam-cinolone acetonide, 2.5 mg. neomycin base, 0.25 mg. gramicidin, and 100,000 units nystatin in PLASTIBASE. References: 1. Shelmire, J.B., Jr.: Monographs on Therapy 3:164 (Nov.) 1958. • 2. Nix, T.E., Jr., and Derbes, V.J.: Monographs on Therapy 3:123 (Nov.) 1958. • 3. Robinson, R.C.V.: Bull. School of Med., U. Maryland 43:54 (July) 1958. • 4. Sternberg, T.H.: Newcomer, V.D., and Reisner, R.M.: Monographs on Therapy 3:115 (Nov.) 1958. • 5. Smith J.G., Jr.; Zawisza, R.J., and Blank, H.: Monographs on Therapy, 3:111 (Nov.) 1958. • 7. Monographs on Therapy, 3:137 (Nov.) 1958. • 8. Howell, C.M., Jr.: North Carolina M.J. 19:449 (Oct.) 1958. • 9. Bereston, E.S.: South. M.J. 50:547 (April) 1957. And whatever the topical corticoid need, a suitable Squibb formulation is available—Kenalog-S Lotion—7½ cc. plastic squeeze bottles. Each cc. supplies 1.0 mg. (0.1%) triamcinolone acetonide, 2.5 mg. neomycin base and 0.25 mg. gramicidin. Kenalog Cream, 0.1%—5 Gm. and 15 Gm. tubes. Kenalog Lotion, 0.1%—15 cc. plastic squeeze bottles. Kenalog Ointment, 0.1%—5 Gm. and 15 Gm. tubes.



Cleared in 5 days



Cleared in 20 days

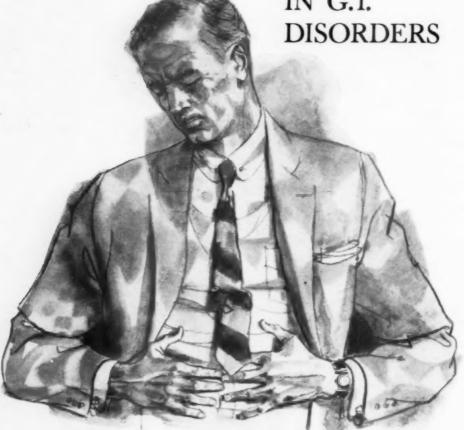


SQUIBB

Squibb Quality - the Priceless Ingredient

"SPECTROCIN'S, "MYCOSTATIN'S, "PLASTIBASE"S, "MYCOLOG"
AND "KENALOG" ARE SQUIBS TRASEMARKS

CONTROLS NERVOUS TENSION IN G.I.



MOST FUNCTIONAL G.I. DISORDERS "can be considered a manifestation of a general psychoneurotic disturbance." (Rossien, A. X.: J. Am. Geriatrics Soc. 5:430, April 1957.)

TREATMENT WITH MILTOWN

- improved control in 15 of 19 cases of common functional G. I. disturbances1
- helped the majority of 23 cases of psychosomatic stomach distress²
- controlled emotional components of spastic colitis,3 chronic ulcerative colitis,4 and psychophysiologic dyspepsia5

ltown

Miltown causes no adverse effects on gastric secretions, emptying time or motility.6

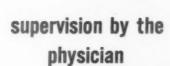
Available in 400 mg. scored and 200 mg. sugarcoated tablets. Also available as MEPROSPAN* (200 mg. meprobamate continuous release cap-

1. Phillips, R. E.: Am. Pract. & Digest Treat. 7:1573, Oct. 1956. 2. Selling, L. S.: J.A.M.A. 157:1594, April 30, 1955. 3. Altschul, A. and Billow, B.: New York J. Med. 57:2361, July 15, 1957. 4. Ross, S. T.: Postgrad. Med. 23:24, Jan. 1958. 5. Tacket, H. S.: Am. Pract. & Digest Treat. 8:597, April 1957. 6. Bodi, T., Wirts, C. W., Jr. and Menduke, H.: Am. J. Gastroenterol. 29:643, June 1958.

WALLACE LABORATORIES, New Brunswick, N. J.

three essential steps
help overweight patients
eat to live,
not live to eat







a balanced eating plan



supportive medication

Obedrin

and the 60-10-70 Basic Plan

provide an effective weight control regimen

Frequently a patient loses weight while on a special diet, then soon gains it back again. Obedrin is a valuable aid to this type of patient. It curbs unhealthy food craving while the patient establishes correct eating habits. Thus he becomes able to maintain optimum weight.

Each capsule or tablet provides:

Semoxydrine® HCl (methamphetamine HCl), 5 mg., for its anorexigenic and mood-lifting effects

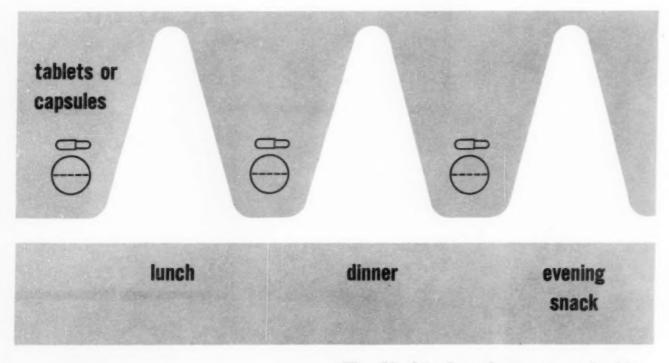
Pentobarbital, 20 mg., to guard against excitation

Thiamine Mononitrate, 0.5 mg., Riboflavin, 1 mg. and Nicotinic Acid (Niacin), 5 mg., to supplement the diet Ascorbic Acid, 100 mg., to help mobilize tissue fluids

Bristol, Tennessee • New York • Kansas City • San Francisco THE S. E. ASSENGILL COMPANY

for <u>dependable</u> control of appetite

... a flexible dosage form



The Obedrin formula permits a flexible dosage schedule which depresses the appetite when it is most important to do so—at peak hunger periods. The physician can adjust the dosage to fit each patient's need.

Obedrin

and the 60-10-70 Basic Plan

advantages of Obedrin

A dependable anorexigenic agent
A flexible dosage form
Minimal central nervous stimulation
Vitamins to supplement the diet
No hazards of impaction

Write for 60-10-70

Write for 60-10-70 menus, weight charts, and samples of Obedrin.

Used with the 60-10-70 Basic Plan, Obedrin offers an ideal weight-control regimen for the overweight patient.

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CLINICAL LITERATURE ON DIGITOXIN CONFIRMS...

"most widely used digitalis preparation"

"drug of choice when a purified

digitalis product is desired"

"the drug par excellence for oral use"

digitaline nativelle

For both initial digitalization and maintenance therapy of the cardiac patient, the steady predictable effect of DIGITALINE NATIVELLE facilitates individualized treatment. Complete absorption from the intestinal tract and uniform dissipation of DIGITALINE NATIVELLE permits easy attainment and maintenance of optimal effects.

Available in oral, intramuscular, and intravenous form with weight for weight equivalence of dosage. A product of Nativelle, Inc.

(1) Gross, H., and Jezer, A.: Treatment of Heart Disease, Philadelphia, W. B. Saunders Company, 1956, p. 41. (2) Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics, ed. 2., New York, The Macmillan Company, 1956, p. 698.(3) Modell, W.: Drugs of Choice 1958-1959, St. Leuis, C. V. Moshy Company, 1958, p. 441.



E. FOUGERA & CO., INC., HICKSVILLE, LONG ISLAND, N. Y.

in just seven months over 2,000,000 patients have received

Madribon

...highly acclaimed because of its 90% effectiveness ...widely accepted because of less than 2% side effects

Madrigid
the 125-mg capsule form of Madribon

Whenever q.i.d. dosage is desirable

ROCHE LABORATORIES Division of Hoffmann-La Roche Inc. Nutley 10, N. J.



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For respiratory and soft tissue infections—In more than 15,000 documented cases, Madribon demonstrated prompt, sustained control of symptoms and rapid disappearance of inflammation and infection . . . with minimal side effects.

For chronic infections—In the longterm treatment of chronic urinary tract infections, a continuing study begun in April, 1958, demonstrated the value of Madribon. A report after six months of daily administration cites the consistent effectiveness of Madribon . . . with no toxic or gastrointestinal manifestations.*

*W. A. Leff, Antibiotic Med. & Clin. Therapy, 6:(Suppl. 1), 44-48, Feb. 1959.

Po Not Confuse it with Tranquilizers-with TranquilizersDean eller

Deaner is a gentle, slow-acting antidepressant—a totally new molecule. It counteracts mild depres-

p-acetamidobenzoic acid salt of 2-dimethylaminoethanol

sion, thereby differing from tranquilizers or sedatives which may aggravate depression.

Deaner is unlike ordinary stimulant drugs in that it gradually leads to increased useful energy and alertness, clearer mentation and emotional normalization.

Deaner does not produce the undesirable side effects of amphetamine-like drugs...no hyperirritability or jitteriness, no excessive motor activity, no loss of appetite, no elevation of blood pressure or heart rate, no letdown on discontinuance.

Deaner is indicated in a wide variety of disturbances associated with or caused by mild depression. It is compatible with virtually all other medications.

Deaner also finds a broad area of usefulness in children with short attention span, behavior problems, and learning defects.

Contraindications: Grand mal epilepsy or mixed types of epilepsy with a grand mal component.

Dosage: Initially, 1 tablet (25 mg.) daily in the morning. Maintenance dose, 1 to 3 tablets; for children, ½ to 3 tablets. Full benefits may require two weeks or more of therapy.

'Deaner' is supplied in scored tablets containing 25 mg. of 2-dimethylamino-ethanol as the p-acetamidobenzoic acid salt. In bottles of 100,

In Mild Depression

and many other emotional and behavioral problems



In hypoprothrombinemia

Rapid action

Wide margin of safety

Versatility of administration

Compatibility

Low dosage forms

rate of absorption faster than menadione or derivatives ... more potent and lasting effects.

substantially safer than vitamin-K analogues - no kernicterus reported.

capsules for oral use...fine aqueous dispersion for parenteral administration.

unlike vitamin-K analogues or similar products, the parenteral form of Konakion is a fine aqueous dispersion compatible with most I.V. vehicles.

no excess, no waste-packaged for economical one-time use.

Prophylactically and therapeutically, Konakion is indicated in obstetrics to prevent or control neonatal hemorrhage, to minimize excessive bleeding in surgery, to offset anticoagulant overdosage, and whenever vitamin-K utilization is impaired.

KONAKION®-brand of vitamin K1 ROCHE® Capsules-5 mg; Ampuls-1 mg/0.5 cc



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reduces anginal attacks and fear of attacks

protects
against pain
by sustained
coronary
vasodilatation
and control
of complicating
and triggering
emotions

reduces fear of attacks
reduces severity of attacks
reduces frequency of attacks
reduces dependence on nitroglycerin
increases workload tolerance

Supplied: Tablets, vials of 50. Each tablet contains 200 mg. of meprobamate and 10 mg. of pentaerythritol tetranitrate.

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Meprobamate and Pentaerythritol Tetranitrate, Wyeth



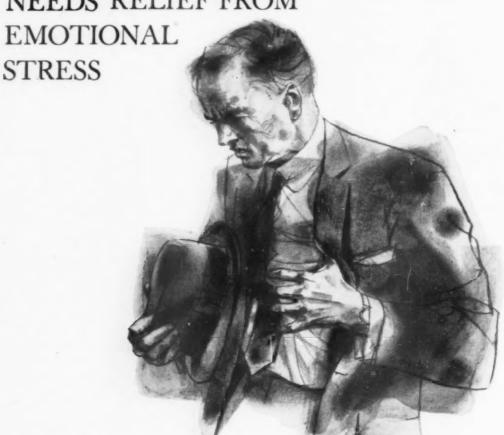
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THE HEART DISEASE PATIENT NEEDS RELIEF FROM



ANXIETY INTENSIFIES the physical disorder in heart disease. "The prognosis depends largely on the ability of the physician to control the anxiety factor, as well as the somatic disease." (Friedlander, H. S.: The role of ataraxics in cardiology. Am. J. Cardiol. 1:395, March 1958.)

TRANQUILIZATION WITH MILTOWN enhances recovery from acute cardiac episodes and makes patients more amenable to necessary limitations of activities.

(Waldman, S. and Pelner, L.: Management of anxiety associated with heart disease. Am. Pract. & Digest Treat. 8:1075, July 1957.)

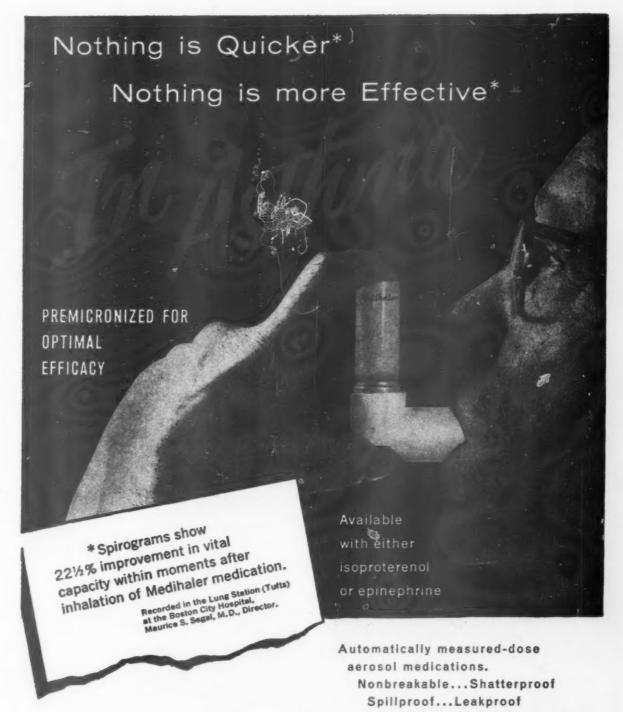
Miltown

meprobamate (Wallace)

Available in 400 mg. scored and 200 mg. sugarcoated tablets. Also available as MEPROSPAN* (200 mg. meprobamate continuous release capsules). In combination with a nitrate, for angina pectoris: MILTRATE*—(Miltown 200 mg. + PETN 10 mg.). *TRADE-MARK CM-7726

Miltown causes no adverse effects on heart rate, blood pressure, respiration or other autonomic functions.

WWALLACE LABORATORIES, New Brunswick, N. J.



Medihaler-ISO°

Medihaler-EPI®

Isoproterenol sulfate, 2.0 mg. per cc., suspended in inert, nontoxic aerosol vehicle. Contains no alcohol. Each measured dose contains 0.06 mg. isoproterenol.

Epinephrine bitartrate, 7.0 mg. per cc., suspended in inert, nontoxic aerosol vehicle. Contains no alcohol. Each measured dose contains 0.15 mg. epinephrine.

- NOTABLY WELL TOLERATED AND EFFECTIVE FOR CHILDREN, TOO-



